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AgrEvo A company of Hoechst and Schering Berlin

FAX

8EHQ-0497-13905

From (Name, Dept., Location)
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To (Name, Dept., Location)
Mr. Ed Gross
US-EPA
Washington, DC

Phone

Fax 2555
202-260-~~7285~~

cc:

Transmitted Pages
(3)

Date
March 18, 1997

Subject: My letter of March 14, 1997 - Your telephone call of today

Dear Mr. Gross:

As you requested, please find attached a copy of the sanitized version of the above mentioned letter.

Thank you for your help and cooperation. Please let me know if you need further assistance.

Sincerely yours,

Joseph A. Conti
Director, Regulatory/Toxicology

JAC/r
epagross.doc

Att.

COMPANY SANITIZED

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A company of Hoechst and Schering Berlin

March 14, 1997

Document Control Officer
Environmental Protection Agency - Mail Code 7407
Information Management Division
East Tower - Basement - Room 99
401 M Street, S.W.
Washington, DC 20460

Subject: Notification of Toxicity Results Which Might Be Reportable Under TSCA 8(e)

To Whom it May Concern:

AgrEvo Environmental Health, Inc. has recently learned about the following toxicology, metabolism and fate study reports for which might be reportable under TSCA 8(e). These studies are summarized in the two attached documents: (1) Data review and evaluation and (2) Dossier on 2. The subject studies are listed below:

Document 1

- 4-Week Feeding Study in the Rat
- 4-Week Feeding Study in the Dog
- 4-Week Feeding Study in the Mouse
- 13-Week Feeding Study in Rats
- 3-Month Feeding Study in Dogs
- 13-Week Feeding Study in Mice
- Percutaneous Route - Cumulative Toxicity (28-Day-Study) - Rat
- Chronic Oral (Feeding) Toxicity and Carcinogenicity in Rats
- 1-Year Feeding Study in the Dog
- Combined Chronic Toxicity and Oncogenicity Study in Mice
- Embryotoxicity and Teratogenicity - Rabbit - Oral Route
- Two-Generation Reproduction in the Rat - Preliminary and Definitive Studies
- Ruminant Feeding Study (Pretest)
- Metabolism in Lactating Goats
- Residue Concentrations in Fat

Document 2

- 8.1.2 Acute and Chronic Toxicity to Daphnia
- 8.1.4 Other Aquatic Organisms - Palaemon aucidens
- 8.2.4 Toxicity to Terrestrial organisms - Honey Bees
- 7.1.1 Anaerobic Degradation
- 7.1.1 Aerobic Aquatic Metabolism
- 7.3 Bioaccumulation

AgrEvo Environmental Health
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AgrEvo A company of Hoechst and Schering, Berlin

Document Control Officer
Environmental Protection Agency - Mail Code 7407
Information Management Division
Washington, DC 20460
March 14, 1997
Page 2

AgrEvo is claiming confidentiality, chemical name, structure and molecular formula because the nature of our research chemistry is considered proprietary. Substantiation of this claims is attached. Sanitized copies of these documents are attached.

is an early stage experimental compound and only very small samples were shipped to AgrEvo researchers for field testing. These researchers will be informed of these data via a revised Material Safety Data Sheet (MSDS). No further handling precautions are deemed necessary at this time, since the company's normal safe handling procedures have mandated all precautions appropriate for chemicals in early research and development stages.

If you have any questions, please feel free to call me at 201-307-3367.

Sincerely yours,

Joseph A. Conti
Director, Regulatory/Toxicology

JAC/r
epatsca2.doc

Attachments

A SANITIZED COPY FOR THE

Compound code/name and structure: COMPANY SANITIZED Sanitized Version Docs 1 & 2	
Chemical name: Chemical class name:	COMPANY SANITIZED
Molecular formula:	$C_{25}H_{29}FO_2Si$
Molecular weight:	408.63
Appearance:	Colorless liquid, practically odorless
Melting point:	Not available

SUBSTANTIATION FOR CLAIMS OF CONFIDENTIALITY

1. For what period of time do you assert this claim of confidentiality? If a claim is to extend until a certain event or point in time, please indicate that event or time period. Explain why the information should remain confidential until such event or time.

   The information should remain confidential indefinitely because it is proprietary information of value to our competitors and because it shows which areas of research our company is involved.

2. Have there been any confidentiality determinations made by EPA, other Federal agencies, or courts in connection with this information? If so, please enclose copies.

   No.

3. Has any of the information that you are claiming as confidential been disclosed to individuals outside your company? If so, what restrictions, if any, apply to use of further disclosure of the information?

   No, disclosure in the future could only occur under a confidentiality agreement.

4. Briefly describe any physical or procedural restrictions within your company relating to the use and storage of the information you are claiming as confidential. What other steps, if any, have you taken to prevent undesired disclosure of the information during its use or when an employee leaves your company?

   Information is kept in a locked file room.

5. Does the information claimed as confidential appear or is it referred to in any of items listed below:

   - advertising or promotional materials for the chemical of the end product containing it;
   - safety data sheets or other similar materials for the chemical or the end product containing it;
   - professional or trade publications; or
   - any other media available to the public or to your competitors.

If you answer yes to any of the above questions, you must indicate where the information appears and explain why it should nonetheless be treated as confidential.

No.

6. Would disclosure of this information be likely to result in substantial harm to your competitive position? If so, you must specifically describe the alleged harmful effects and indicate why they should be considered to be substantial. Also, you must describe how disclosure of the information would cause the harm.

Yes. Disclosure of the information would alert our competitors to active molecules discovered by our company and would give them a possible competitive position by allowing them to research similar areas of chemistry.

7. If the information in question is "health and safety data" pursuant to 40 CFR PART 2.306(3)(i), do you assert that disclosure of the information you are claiming as confidential would reveal:

a) confidential process information;

b) confidential proportions of a mixture; or

c) information unrelated to the effects of the substance on human health or the environment?

No health and safety data are involved.

Study Title

Data review and evaluation of toxicological and metabolism studies on the technical substance

Authors

Dr. E. Ebert
Dr. K.-H. Leist

Completed

22 Juni 1995

Testing Facility

Hoechst Schering AgrEvo GmbH
Toxicology - Frankfurt
D-65926 Frankfurt am Main
Germany

Report No.

95.0402

CONTENTS

1. METABOLISM STUDIES IN MAMMALS

1.1 Absorption, distribution and excretion studies following both oral and percutaneous administration

Rat - single oral application (Büttner et al. 1991,1992; Eckert & Kellner 1989, 1990; Kellner & Puttkamer 1993a)

Excretion data were obtained in rats after single oral application of 10 to 500 mg kg body weight. Normally 60 to 90% of the applied radioactivity was excreted after 24 hours, and recovery after 7 days was greater than 95%. Up to 4% of the administered amount was still present in the organs after 7 days. The predominant portion (> 90%) was excreted via faeces and only 1 to 3.5% via urine, with higher values among the male rats. Excretion in most cases was biphasic, with mean half-lives of 7 and 30 hours, the times for faeces and urine being about the same.

Rat - repeated oral administration (Kellner et al. 1993b)

The rapid elimination was also evident during the repeated treatment studies (10 x 10 mg/kg and 10 x 500 mg/kg body weight, ten times radiolabelled), in which about 90% of the hitherto administered amount were excreted within 24 hours. Up to 5% of the administered amount was still present in the organs after 7 days. Renal and faecal elimination was similar to that in single dose studies, but it was delayed after repeated administration.

Gastro-intestinal (oral) absorption (Büttner 1992; Kellner et al. 1993b)

All kinetics and metabolism studies conducted with generally indicate a low rate of oral absorption. Based on a special absorption and biliary excretion study in female rats (Büttner 1992), biliary excretion plays a relevant role in the excretion of absorbed ; however, the result of this study (about 5 % absorption) must be considered to be of very limited value with respect to the quantitative aspects, because the experiment was performed with narcotised rats, the very limited physiological activity of which resulted in artificially low absorption. A situation of this kind may present major problems and uncertainties when it comes to estimating the biliary excretion rate of absorbed material, particularly in studies where the amounts of the compound incorporated in the organ and tissues are determined a relatively long time after oral administration.
Based on these considerations and with a view to an assessment of human health risk resulting from prolonged low-dose exposure, the study of Kellner et al. 1993b appears to be the most appropriate for an estimation of gastro-intestinal absorption :
On the basis of the radioactivity measurements in urine and tissues/organs after repeated oral application of low (10 mg/kg) doses determined 4 hours after the last dosing, the minimum oral absorption rates (tissue excl. gastro-intestinal tract plus urine) were estimated to be 13.2 and 12.4 % in the female and male rat, respectively. The corresponding values from the high (500 mg/kg) dosing were considerably lower (less than 4 %).
The relevant data of this study are summarised in the following table :

INTRODUCTION

is a new insecticide developed by Hoechst Schering AgrEvo GmbH. is intended for use as a preventive wood protective chemical. The chemical structure is given in the following figure:

Figure 1: chemical structure

Molecular weight: 408.63

has a high partition coefficient for octanol/water (log P_{OW}) of 8.2. In the following pages the information related to the toxicity and metabolism data will be reviewed to assess the toxicological profile of with a view to a classification and labelling proposal in accordance with the principles of Commission Directive 93/21/EEC of 27 April 1993 adapting to technical progress for the 18th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances.

All studies reviewed below were conducted in compliance with the GLP principles and fulfil the requirements of the corresponding EEC and OECD testing guidelines.

Minimum oral absorption rate (%) in the rat following repeated (10 times) oral exposure						
	low dose (10 mg/kg b.w.)			high dose (500 mg/kg b.w.)		
rat	urine	tissues	absorption	urine	tissues	absorption
male	3.91	8.5	12.4	1.66	2.08	3.7
female	0.64	12.53	13.2	0.6	3.2	3.8
radioactivity found 4 hours after the last (10th) dosing						

Rat - single percutaneous administration (Till C. P., 1992)

Absorption of ^{14}C-labelled was studied in 72 male rats following single dermal application of 0.001, 0.01 and 0.11 mg / cm² (dose per animal) in the form of 00 EC76, a representative emulsifiable concentrate formulation. Each dose group consisted of 24 animals which were killed in subgroups of 4 animals after exposure times of 0.5, 1.0, 2.0, 4.0, 10 and 24 hours . The percentage dose absorbed, as measured by the direct method, was rather variable over the 24 hour period as shown in the table below.

nominal dose	dermal absorption (% applied dose) after 24 hours of exposure				
mg / cm² skin	urine	faeces	carcass	total	recovery
0.1	0.37	0.13	5.71	6.23	83
0.01	0.23	0.08	2.51	2.82	92
0.001	0.51	0.23	11.46	12.25	93

For an assessment of human health risk resulting from prolonged low-dose exposure, the dermal absorption rate of 12.25 % determined at the lowest dose level appears to be the most appropriate value.

1.2. Elucidation of metabolic pathways (for references see section 1.1.)

The main component in faeces is making up 60 to 80% of the applied amount. Up to 10% of the applied amount are present in the form of the de-ethylated metabolite . The other (unknown) metabolites in faeces are in each case considerably less than 10%.

In urine, and are found in free and conjugated (sulphate) form. However, in view of the small amounts excreted via urine and their ready solubility in water, they are of no significance for the overall residue pattern.

In general it should be noted that, if the applied amount is taken as the reference magnitude, is a substance which metabolises only to a very low extent. However, if the absorbed portion is taken into account, it will be seen that this is almost completely metabolised. Most of the metabolites are excreted via the faeces, since only was present in faeces after fistulisation of the bileduct. In the faeces from day 2 onwards (not relevant from the quantitative viewpoint), the metabolite portion increased relative to intact active ingredient (Büttner et al. 1992).

1.3. Biokinetics and metabolism in farm animals

Ruminant feeding study (Pretest) (Zietz & Spranz 1992)

Two diary cows received daily in doses equivalent to 1 or 10 mg/kg diet (ppm) over a period of 10 weeks. The high-dose cow was killed 1 day after the last dosing, the low-dose cow after a depuration period of 23 days. During the treatment and depuration period two milk samples were taken daily and analysed for residues. After slaughtering, tissue samples of fat, muscle, diaphragm, liver, kidneys and blood were also analysed for residues. The plateau concentration in milk was reached very rapidly, i.e. two days after the commencement of treatment. Except in fat tissue, no - or only negligible tissue residues were found. The residues in the milk (plateau average concentration) and body fat are shown in the following table :

	examination time	residue concentration (ppm)			bioconcentration factor (BCF)		
		body fat	milk fat	milk	body fat	milk fat	milk
Cow 1 (1 ppm)	plateau concentration	-	0.7	0.03	-	0.7	0.03
	23 day p.a.	0.36	< DL	< DL	0.36		
Cow 2 (10 ppm)	plateau concentration		8.9	0.35		0.89	0.035
	1 day p.a.	5.8	-	-	0.58	-	-

ppm = mg/kg; p.a. = after the end of treatment; < DL = below detection limit of 0.005mg/l

These results indicate a transfer of into the cow milk fat at concentrations slightly higher than those in the body fat. However, due to a fat content of about 5 % in the milk, the concentration of the milk must be considered to be very low in view of the BCF values of 0.03. In addition, it is worth noting that the residue level in milk fat declined rapidly after the termination of treatment and after 3 days declination period no residues could be detected; this observation permits the conclusion that no or very low amounts of may be released from the body fat into the milk under normal intuitive conditions.

Metabolism in lactating goats (van Dijk A. 1992)

In this study, lactating goats received ^{14}C- labelled on three consecutive days at a dose level of 5.3 mg/kg body weight to elucidate the absorption, distribution, metabolism and excretion. In addition, the concentration profile of radioactivity in milk and the excretion pattern via urine and faeces were monitored. Two hours after the last dosing the animals were killed for elucidation of residues in edible tissues.

The excretion of mainly proceeded via the faeces. Only low amounts were excreted in urine (0.8%) and milk (1.3%). The highest ^{14}C-levels were found in the liver (76 ppm) and at a considerably lower level in milk (2.9 ppm), kidneys (2.4 ppm), fat (1.3 ppm) and muscle (0.7 ppm).
In the other organs and in the milk, only parent compound was detected.

1.4. Residues of in adipose and other tissues of mammalian species

has a high partition coefficient for octanol/water (log P_{ow}) of 8.2. For this reason it had been expected to accumulate in fat, and a series of studies and residue analyses in connection with toxicity studies in rat, mouse and dog were conducted to determine the bioconcentration factor (BCF). The BCF is defined as the quotient of the test substance concentration in fat and administered diet.

Residue concentrations in fat :

Considerably high residue concentrations of were measured in adipose tissue at all examination times. However, the plateau (steady-state) concentrations at the different dosing levels were reached within an exposure period of 3 to 12 months. The residue concentrations measured in the different dosing groups showed a clear dose-dependency. In general, the residue concentrations in dogs and mice were comparable in both sexes, but in the rat frequently somewhat higher in the females. Particularly during the first 52 weeks of exposure, no relevant differences could be observed between subcutaneous and retroperitoneal fat, although the residues in retroperitoneal fat were often slightly higher than in subcutaneous fat. The following table summarises the residues in fat after low dose exposure obtained in the different toxicological or special residue studies.

type of study	diet	plateau concentration			elimination	reference
	(ppm)	time (month)	ppm	BCF	half-life (day)	
accumulation rat, female*	5	12*-14*	13* 20*	2.7*-3.9*	39*-47*	Idstein 1994
2-year toxicity rat	400	9	1147	2.9	ND	Simonnard & Provot 1995a
2-year toxicity mouse	400	3	1936	5	ND	Simonnard & Provot 1995b
1-year toxicity dog	60	6	246	4.1	ND	Stammberger 1994
1-year toxicity dog	320	6	1681	5.3	ND	Brunk 1992
multigeneration rat, P dam	200	ND	718	3.6	ND	Dotti & Müller-Kallert 1993
4-wk dermal toxicity rat	100 *	ND	53	0.5	27	Ebert 1994

- = no tissue taken; * = mg/kg b.w.; ND = not determined; * = subcut. fat; * = retroperitoneal fat; * = calculated values;

Residues in fat were eliminated rapidly ($T_{1/2}$ = 4 - 8 days) after single dosing, but considerably more slowly ($T_{1/2}$ = 13 - 182 days) after repeated dosing. Plateaus were reached after 3 to 12 months during prolonged feeding. Elimination half-lives of 39 - 47 days were obtained in a chronic rat feeding study (5 mg/kg diet). The BCF values derived from chronic toxicity studies in different species were comparable and ranged from 3-5.
In the other organs and tissues only very low residue levels were found resulting in BCF values of much less than 0.1 (liver, kidneys, testes) and less than 0.01 (brain).

A detailed review of the toxicokinetic and metabolism studies is given in a document prepared by Stumpf 1995.

2. ACUTE TOXICITY

2.1. - 2.5. Acute Toxicity

Acute testing of yielded the following results:

Species	Sex (No./dose)	Doses (mg/kg')	Purity	Vehicle	LD/LC*50 (mg/kg')	Reference
2.1. oral						
rat	M/F (5)	5000	95.4 %	sesame oil	> 5000	Diehl & Leist 1987a
2.2. percutaneous						
rat	M/F (5)	5000	95.4 %	original	> 4000	Diehl & Leist 1987b
2.3. inhalation						
rat	M/F (5)	6.61*	96.8 %	aerosol	> 6.61*	Hofmann & Jung 1988
2.4. intraperitoneal						
rat	M/F (5)	2000	96.8 %	sesame oil	> 2000	Diehl & Leist 1988a
2.5. other species						
mouse, oral	M/F (5)	5000	96.8 %	sesame oil	> 5000	Diehl & Leist 1987c
rabbit, dermal	M/F (5)	4000	95.4 %	original	> 4000	Diehl & Leist 1988b
* mg/l air; highest applicable concentration due to technical reasons						

No lethality occurred at the tested limit dose or the maximum applicable dose in any of the studies. Following oral exposure slight non-specific signs of intoxication occurred in the form of reduced spontaneous activity, prone position or contracted flanks on the day of application only; during the inhalational exposure a slight respiratory disturbance and narrowing of the palpebral fissure were observed. Following percutaneous and intraperitoneal exposure no clinical signs were noted. Necropsy revealed only changes following i.p. application in the form of white deposits in the abdominal cavity and on the liver and marked injection of blood vessels in the gastro-intestinal tract. In one animal, the stomach was adhering to the liver.

2.6. Eye Irritation

Eye irritation potential of (95.4% purity) was investigated in nine albino rabbits according to the US-EPA guidelines (1984) § 81-4 "Primary eye irritation". The eyes of six rabbits were flushed after 24 hours, the eyes from the another three rabbits one minute following treatment. In the eyes flushed after 24 hours silafluofen caused mild to moderate irritancy after one and 24 hours in the form of conjunctival redness and chemosis which proved to be completely reversible after three days. In the eyes flushed after one minute the irritating potency was less pronounced (Diehl & Leist 1987d). According to the current EEC evaluation principles the following mean score was calculated :

	group mean score for days 1 to 3			
Ocular lesion	cornea opacity	iris	conjunctival redness	conjunctival chemosis
Test substance	0	0	0.66	0
Irritating (EU)	$\geq 2 \leq 3$	$\geq 1 \leq 1.5$	≥ 2.5	≥ 2

Based on these scores, the test substance is not subject to the labelling requirement "Irritating to the eye" according the criteria for classification in Directive 93/21/EEC.

2.7. Skin Irritation

Skin irritation potential of was investigated in six albino rabbits according to the US-EPA guidelines (1984) § 81-5 "Primary dermal irritation". caused mild irritancy after one and 24 hours in the form of erythema which proved to be completely reversible after three days; no oedema was noted (Diehl & Leist 1987e). According to the current EEC evaluation principles the following mean score was calculated :

	group mean score for days 1 to 3	
Dermal reaction	erythema	oedema
Test substance	0.22	0
Irritating (EU)	$\geq$ 2.0	$\geq$ 2.0

Based on these scores, the test substance is not subject to the labelling requirement "Irritating to the skin" according the criteria for classification in Directive 93/21/EEC.

2.8. Skin Sensitisation

To assess contact sensitisation in guinea-pigs the modified Buehler method was used. As an induction phase, the guinea-pigs were exposed for 6 hours dermally under an occluded patch three times a week for three weeks to original (undiluted) The animals were challenged with original on the third week after the final induction exposure. Ten control (physiological saline) and 20 guinea-pigs treated with the test substance were used in this study. None of the animals treated with exhibited a positive reaction to the challenge treatment. Thus, proved to be non-sensitising (Diehl & Leist 1988c).

In another sensitisation test was also tested in the Guinea-pig Maximisation Test (GMPT) and proved to be non-sensitising. As an intradermal induction phase, 20 animals received injections of a 0.5 % dilution in petrolatum, for dermal induction and challenge exposure the animals were treated with undiluted test substance. This study comprised 10 controls. None of the animals treated with exhibited a positive reaction to the challenge treatment (Schollmeier & Leist 1988a).

Testing for photosensitising properties was conducted using a negative control (0.1 % DAE_{333}), positive control (chlorpromazine) and a testing group , each consisting of 10 guinea pigs. and chloropromazine were applied in the form of 0.1 % DAE_{333} solution and the dosing volume was 0.1 ml. After dermal exposure the animals were treated for 7 minutes with light of wavelength > 315 nm on 4 days during the first week. At the beginning of the second week, Freund's Adjuvant was applied intradermally into four corners of the irradiation area. During both the second and third week, the animals were irradiated on 4 days for 7 minutes at a wavelength of > 280 nm. For challenge treatment, the animals were treated as in the first week, but were irradiated on 3 days for 2 minutes with light of wavelength > 280 nm.

After challenge treatment none of the animals in the negative and test substance group showed a photoallergenic reaction. In the positive control group 7 out of 10 animals exhibited positive reactions, thus verifying the sensitivity of the test system (Schollmeier & Leist 1989a).

Based on the results obtained in different sensitisation tests is not subject to the labelling requirement according the criteria for classification in Directive 93/21/EEC.

3. SHORT-TERM TOXICITY

3.1. Oral cumulative toxicity (4-week studies)

4-week feeding study in the rat (Diehl & Leist 1988e)

purity 96.8 %) was administered orally to 5 groups, each composed of 5 male and 5 female Wistar rats over a period of 28 days in the daily diet at concentration levels of 0 - 80 - 400 - 2000 or 10000 mg/kg (ppm) diet. Satellite groups consisting of 5 males and 5 females were treated analogously at 0 - 2000 or 10000 ppm, but sacrificed two weeks after termination of the treatment. These concentrations were equivalent to a mean daily substance intake (mg/ kg body weight) of 8.5, 44, 209 and 1019 (males) and 8.0, 41, 195 and 947 (females).

caused a marginal inhibition of body weight gains among the males in the highest treatment group. In addition, the liver weight was moderately increased in the females from the highest dosing group; an effect which proved to be reversible by the end of a 2-week recovery period. No other changes attributable to , in particular changes indicative of an impairment of haematology (red blood cell parameters) or male reproductive organs were noted in any treated group.
Based on these results, the NOEL is considered to be 2000 ppm, equivalent to a mean daily substance intake of 198 mg/kg body weight.
The changes / data in the liver weight and haematology (red blood cell parameters) are summarised in the following table :

			Dose (mg/kg diet)				
Parameter	Duration	Sex	0	80	400	2000	10000
Liver weight (%)	4 wk	M	3.6	3.8	3.7	3.6	3.8
		F	3.3	3.9	4.1	4.1	4.8*
	recovery	M	3.6	-	-	3.8	3.7
	2-wk	F	3.6	-	-	3.9*	3.8
Haematology	4-wk						
RBC		M	7.7	7.4	7.8	7.7	8.1
		F	7.3	7.5	7.6	7.4	7.4
Hb		M	145	145	152	147	160*
		F	139	143	145	142	140
Ht		M	0.45	0.45	0.46	0.44	0.49
		F	0.43	0.44	0.45	0.43	0.43

RBC = erythrocytes 10^{12}/l; Hb = haemoglobin (g/l); Ht = haematocrit
* = significantly different from the control ($p \leq 0.05$)

4-week feeding study in the dog (Brunk, 1988)

(purity 96.8%) was fed in the daily diet to groups of 3 male and 3 female Beagle dogs at concentration levels of 0 - 320 - 1600 or 8000 mg/kg diet (ppm).
Food consumption appeared to be impaired in one male and one female from the highest dose group (8000 ppm); however, no changes in body weight could be observed. Based on the laboratory examinations, the liver and the red blood cells proved to be the target organs: caused an increase in alkaline phosphatase activity at the two highest treatment levels; and also an increase in ALAT (GPT) in two males from the 8000 ppm group. In addition, the absolute (15-23%) and relative (24-29%) liver weight were increased as compared with the controls at 8000 ppm. Although no pathological findings were established by histology, these findings were considered to be an indicator to liver damage. With regard to the red blood cell parameters, a slight decrease in erythrocytes was observed at the 1600 and 8000 ppm dosing levels. In addition, haemoglobin content and haematocrit were reduced in the 8000 ppm dose group.
Based on these results the NOEL can be established at a dietary level of 320 ppm, equivalent to a daily substance intake of approximately 19.3 (19.9 males/ 18.7 females) mg/kg body weight.
The changes in the liver (weight, alkaline phosphatase) and haematology (red blood cell parameters) are summarised in the following table:

				Dose (mg/kg diet)			
Parameter	Duration	Sex	No.	0	320	1600	8000
Liver weight (%)	4-wk	M&F	6	3.22	3.19	3.72	4.06*
Alkaline phosphatase (U/l)	4-wk	M	3	112	113	262	462
		F	3	119	130	304	613
		M&F	6	116	122	283	538
Haematology	4-wk						
RBC		M&F	6	7.56	7.11	6.83*	6.73*
Hb		M&F	6	172	156	158	154*
Ht		M&F	6	0.54	0.51	0.49	0.47*

RBC = erythrocytes (10^{12}/l); Hb = haemoglobin (g/l); Ht = haematocrit;
* = significantly different from the control ($p \leq 0.05$);
Note : According to the report statistical analysis was carried out in the case of liver weights and haematology on the basis of pooled males and female values; no statistical analysis was performed in the case of alkaline phosphatase.

4-week feeding study in the mouse (Diehl & Leist 1988f)

(purity 96.8 %) was administered orally to 5 groups, each composed of 5 male and 5 female NMRI mice, in the daily diet at concentration levels of 0 - 80 - 400 - 2000 or 10000 mg/kg (ppm) diet over a period of 28 days. Satellite groups, consisting of 5 males and 5 females, were treated in the same way at 0 - 2000 or 10000 ppm, but sacrificed two weeks after termination of treatment. These concentrations were equivalent to a mean daily substance intake (mg/kg body weight) of 15.9, 87, 471 and 1937 (males) and 18.5, 102, 514 and 2552 (females).

The liver weight was slightly increased at 10000 ppm. This effect proved to be reversible by the end of the 2-week recovery period. The slightly higher liver weights at 2000 and 10000 ppm in the females after the 2-week recovery period are considered to be related to the low control value. Clinical chemistry parameters indicative of an impairment of the hepatic functions such as GOT, GPT or alkaline phosphatase were not measured in this study due to the limited amount of serum available. The haematology parameters indicated no changes in the sense of anaemia.
Based on a slight increase in liver weights at 10000 ppm, the No Observable Effect Level (NOEL) is considered to be 2000 ppm; this dietary level was equivalent to a mean daily substance intake of 472 and 514 mg/kg body weight in the males and females, respectively.

The changes in the liver weights and red blood cell parameters are summarised in the following table:

			Dose (mg/kg diet)				
Parameter	Duration	Sex	0	80	400	2000	10000
Liver weight (%)	4-wk	M	4.7	4.9	4.9	5.2	5.7*
		F	4.4	4.5	4.4	4.9	5.1*
	recovery 2-wk	M	4.9	-	-	5.0	4.7
		F	4.2	-	-	4.9*	4.7*
Haematology/RBC	4-wk						
		M	9.4	9.2	9.5	9.2	9.5
		F	9.3	9.4	9.7	9.2	9.2
Hb		M	174	169	178	171	174
		F	174	176	182	173	170
Ht		M	0.50	0.49	0.51	049	0.49
		F	0.50	0.49	0.52	0.48	0.48
Reticulocytes		M	0.084	-	-	-	0.072
		F	0.082	-	-	-	0.077

RBC = erythrocytes (10^{12}/l); Hb = haemoglobin (g/l); Ht = haematocrit
* = significantly different from the control ($p \leq 0.05$)

3.2. ORAL ADMINISTRATION (90-DAY STUDY)

13-week feeding study in rats (Schollmeier & Leist 1989b)

(purity 96.8 %) was administered to 5 groups, each composed of 10 male and 10 female Wistar rats, in the daily diet at concentration levels of 0 - 80 - 400 - 2000 or 10000 mg/kg (ppm) diet over a period of 13 weeks. Satellite groups, consisting of 10 males and 10 females, were treated in the same way at 0 - 2000 or 10000 ppm, but sacrificed four weeks after termination of the treatment. These concentrations were equivalent to a mean daily substance intake (mg/kg body weight) of 6.7, 33, 166 and 827 (males) and 7.0, 35, 170, and 819 (females).

caused slight to moderate increases in liver weights at 10000 ppm in both sexes; this effect was largely reversible after 4 weeks of recovery. No histopathological changes were observed. In addition, slight decreases in erythrocytes, haemoglobin content and haematocrit values were observed in the males from the highest dosing group at the end of the treatment period; this change, which could

not be detected at the end of the 4-wk recovery period, may possibly have been treatment-related. No other changes attributable to the test substance were found in any of the treated groups.
Based on the liver and marginal haematology findings, the NOEL is considered to be 2000 ppm (diet), equivalent to a mean daily substance intake of 168 mg/kg body weight.

Note: A slight decrease in testicular weight at 2000 and 10000 ppm was seen at the end of treatment and more marked at the end of the 4-wk recovery period at 10000 ppm. In addition, four males - two males each of the main and recovery groups - showed tubular atrophy (grade 1 and 3); only one control (recovery) was noted with this finding (grade 1).

The changes in liver weight and haematology (red blood cell parameters) are summarised in the following table:

			Dose (mg/kg diet)				
Parameter	Duration	Sex	0	80	400	2000	10000
Liver weight (%)	13-wk	M	3.2	3.3	3.4	3.5	3.8*
		F	3.2	3.5	3.3	3.5	3.7*
	recovery	M	3.0	-	-	3.1	3.2*
	4-wk	F	3.2	-	-	3.1	3.3
Haematology	13-wk						
RBC		M	8.4	8.3	8.4	8.3	8.0*
		F	7.9	7.8	7.6	8.1	7.7
Hb		M	150	150	152	149	146
		F	142	141	137	143	142
Ht		M	0.45	0.44	0.46	0.44	0.42*
		F	0.43	042	0.42	0.45	0.42

RBC = erythrocytes 10^{12}/l; Hb = haemoglobin (g/l); Ht = haematocrit
* = significantly different from the control ($p \leq 0.05$)

3-month feeding study in dogs (Brunk, 1989)

Groups of beagles (4 animals/sex/group) received (95.8 %) at dietary levels of 0 - 320 - 1600 or 8000 ppm for 3 months. Satellite groups consisting of 2 males and 2 females were treated analogously at 0 - 1600 or 8000 ppm, but sacrificed four weeks after the termination of treatment.

Feeding at 320, 1600 and 8000 ppm over a period of 3 months caused a moderate to marked increase in liver weights in both sexes; in addition, the activity of the alkaline phosphatase (ALP) and ALAT (GPT) were increased at the 8000 ppm level. A clear tendency of increased alkaline phosphatase was already recognisable in the 1600 ppm dosing group. Determination of ALP after 6-wk treatment revealed a dose-dependent increase from 320 ppm onwards in the males and from 1600 ppm onwards in the females; GOT and GPT values were also increased at the highest dose level. All other changes proved to be completely reversible after 4 weeks of recovery, except for the ALP value in the highest dose group. Although no corresponding pathological changes were observed, these findings are considered to be indicative of liver damage. With regard to the red blood cell parameters, slight decreases in erythrocytes, haemoglobin content and haematocrit were observed in both sexes at the 1600 and 8000 ppm dosing levels at the end of treatment. This effect was not detectable after the 4-wk recovery

period. Measurement after a 6-wk treatment period revealed only faint signs of this effect at the 8000 ppm level. In addition, there was a higher frequency in diarrhoea in both these groups and some of the dogs in the highest dose group showed a temporary impairment of food consumption.

Based on the increases in liver weights in connection with the increase in ALP, a NOEL of slightly less than 320 ppm can be derived; this is equivalent to a mean daily substance intake of less than 22.8 (24.1 males/ 21.5 females) mg/kg body weight for both sexes.

The changes in the liver (weight, alkaline phosphatase) and haematology (red blood cell parameters) are summarised in the following table:

				Dose (mg/kg diet)			
Parameter	**Duration**	**Sex**	**No.**	**0**	**320**	**1600**	**8000**
Liver weight (%)	13 wk	M&F	8	2.95	3.70*	3.76*	4.54*
	4-wk recovery	M &F	4	3.45	-	3.33	3.41
Alkaline phosphatase (U/l)	6 wk	M	6	192	273*	327*	739*
		F	6	192	199	351*	689*
	13 wk	M	6°	179	212	296	872*
		F	6°	154	155	310	689*
	4-wk recovery	M	2	106	-	124	324
		F	2	117	-	123	226
ALAT(GPT) (U/l)	6 wk	M	6	17	16	17	45*
		F	6	18	16	15	51
	13 wk	M	6°	22	21	37	43*
		F	6°	21	19	22	39*
	4-wk recovery	M	2	24	-	22	28
		F	2	16	-	21	26
Haematology	6-wk						
RBC		M&F	12	6.68	6.59	6.36	6.12
HB		M&F	12	151	150	146	139*
HK		M&F	12	0.47	0.47	0.46	0.44*
Haematology	13-wk						
RBC		M&F	12	6.93	6.65	6.26*	6.21*
HB		M&F	12	154	149	143*	142*
HK		M&F	12	0.49	0.46	0.45	0.44*
RBC	4-wk recovery	M&F	4	6.60	-	6.45	6.64
HB		M&F	4	151	-	147	152
HK		M&F	4	0.49	-	0.46	0.48

RBC = erythrocytes (10^{12}/l); Hb = haemoglobin (g/l); Ht = haematocrit
* = significantly different from the control ($p \leq 0.05$)
° = no. of animals at 320 ppm = 4;

13-week feeding study in mice (Schollmeier & Leist 1989c)

(purity 96.8 %) was administered orally to 5 groups, each composed of 10 male and 10 female NMRI mice, in the daily diet at concentration levels of 0 - 80 - 400 - 2000 or 10000 mg/kg (ppm) diet over a period of 13 weeks. These concentrations were equivalent to a mean daily substance intake (mg/kg body weight) of 14, 70, 338 and 1668 (males) and 15, 70, 353 and 2003 (females).

caused a moderate increase in liver weights at 10000 ppm in both sexes; however, no histological correlate was found. Remark: Clinico-chemical parameters indicative of an impairment of the hepatic functions such as GOT, GPT or alkaline phosphatase were not measured in this study due to the limited amount of serum available.

Haematology revealed a slight decrease in erythrocytes, haemoglobin and haematocrit value and a marginal increase in reticulocytes in the males from the highest dosing group. No other substance-related changes were established.

Based on these findings, the NOEL was established at a concentration of 2000 ppm, equivalent to an average daily substance intake of 338 and 353 mg/kg body weight in the males and females, respectively.

The changes in the liver weight and red blood cell parameters are summarised in the following table:

			Dose (mg/kg diet)				
Parameter	Duration	Sex	0	80	400	2000	10000
Liver weight (%)	13 wk	M	4.0	3.8	4.0	3.9	4.7*
		F	3.8	3.7	4.0	4.0	5.8*
Haematology	13 wk						
RBC		M	9.4	9.0	9.1	9.2	8.7*
		F	9.3	9.3	9.1	9.1	9.1
Hb		M	175	171	172	169	163*
		F	175	174	172	172	172
Ht		M	049	0.47	0.47	047	0.44*
		F	0.49	0.49	0.48	0.48	0.48
Reticulocytes		M	0.037	-	-	-	0.043*
		F	0.037	-	-	-	0.038

RBC = erythrocytes (10^{12}/l; Hb = haemoglobin (g/l); Ht = haematocrit

3.3. OTHER ROUTES

Inhalation route

A short-term inhalation study in rats was not conducted, because human exposure to via the inhalation route is unlikely for the following reasons:

The vapour pressure of is very low, i.e. 5.5×10^{-6} at 25 °C (Grewer 1988) and thus no relevant inhalation exposure of vapour is possible.

is an oily liquid; therefore the formation of inhalable fine dust is not possible.

Percutaneous route - cumulative toxicity (28-day study) - rat

Preliminary study (Schollmeier & Leist 1988)

In a cumulative dermal toxicity study in rats (96.8%) was applied without a carrier on five consecutive days - each for 6 hours/day - to the shaved nape skin under an occlusive bandage. Two groups, each composed of 6 male and 6 female rats, were treated at dose levels of 0 or 1000 mg/kg body weight. After the final dermal treatment the animals were kept under observation for another 3 days. Clinical observations, food consumption, body weight and necropsy indicated no changes attributable to the treatment.

Main study (Ebert, 1994)

In a repeated-dose dermal toxicity study in rats - 21 applications, each for 6 hours/day, 5 days per week over a period of 30 days - was applied to the shaved nape skin under an occlusive bandage. Four groups, each composed of 5 male and 5 female rats, were treated at dose levels of 0 - 100 - 300 or 1000 mg/kg body weight, using PEG 400 as vehicle. Satellite groups of 5 males and 5 females were treated analogously with 0 - 300 or 1000 ppm, but sacrificed four weeks after the termination of treatment.

No findings of toxicological significance could be detected in any testing group at the end of the 4-week treatment period. In addition, in the form of an emulsion in PEG 400 proved to be non-irritating to the treated skin area. At the end of the 4-week recovery period the testicular weights showed a tendency to decrease by about 10-15% as compared with the control, resulting in a statistically significant change in the relative organ weight. Taking into account the slight degree of the changes and the absence of any dose-dependency, the significance of the finding was considered to be doubtful.

Thus, the No Observable Adverse Effect Level (NOAEL) for systemic toxicity was considered to be 1000 mg/kg body weight per day.

Note : In addition, the concentrations of were measured in adipose tissue. The results of these examinations are reported under section "1.4.".

4. CHRONIC ORAL TOXICITY AND CARCINOGENICITY

4.1. **Chronic oral (feeding) toxicity and carcinogenicity in rats** (Simonnard, 1992)

In a combined chronic toxicity and carcinogenicity study, (lots of 94.0 and 95.4% purity) was fed to Sprague-Dawley rats (110 males and 110 females/group) in the diet at concentrations of 0, 400, 2000, 10000 or 20000 ppm for two years. These concentrations were equivalent to a mean daily substance intake (mg/kg body weight) of 20, 101, 500 and 1022 (males) and 26, 130, 661 and 1335 (females). Twenty rats per sex and group were killed after 12 months and 24 months respectively in order to evaluate chronic toxicity. Fifty rats per sex and group were scheduled for sacrifice after 104 weeks to evaluate the carcinogenic potential. Further 20 rats per sex and group were scheduled for residue determinations in various tissues at different times in view of the lipophilic nature of ; this part of study is reported under section 1.4.

Treatment at 10000 and 20000 ppm caused a slight to moderate increase in the frequency of clinical signs (round back, emaciation, chromorhinorrhoea, soft faeces) in the males, decrease in food consumption and body weight gain and decrease in triglycerides (including at 2000 ppm) and increase in cholesterol (females only).

Organ weight analysis and pathology identified the liver and male reproductive organs (testes and epididymides) as target organs. No changes attributable to the test substance were observed in the red blood cell parameters at any of the examination times.

An increase in liver weight together with centrilobular hepatic cell hypertrophy was found in both sexes at 2000 ppm and higher dose levels.

The effects on the male reproductive organs consisted in an increase in soft consistency and reduction in size of testes and epididymides associated histologically with degeneration of seminiferous tubules and inhibition of spermatogenesis in the testes and oligospermia and small tubules in the epididymides from 2000 ppm onwards; there was also an decrease in testicular weight at 10000 and 20000 ppm.

An increase in foamy alveolar macrophages in the lungs was also noted at 2000 ppm and higher doses after 104 weeks, but only in the females.

Based on these results the NOAEL was considered to 400 ppm, which is equivalent to a mean daily substance intake of 20 mg/kg body weight. No indication of any carcinogenic potential was found up to and including the 20000 ppm level.

The changes in the liver, testes and lungs are summarised in the following table:

104-wk rat study - toxic effects

Parameter	Duration	Sex	No.	Dose (mg/kg diet) 0	400	2000	10000	20000
LIVER Weight (%)	52 wk	M	10	2.9	3.0	3.2	3.5*	3.6*
		F	10	2.8	3.1	3.5*	4.1*	4.1*
	104 wk	M	10	2.4	3.0	2.5	2.7	3.2*
		F	10	2.9	3.2	3.3	4.2*	4.1*
Pathology Hypertrophy	52 wk	M	20	/	/	/	13	12
		F	20	/	/	/	11	17
	104 wk	M	70	/	/	18	31	27
		F	70	/	/	38	59	50
TESTES Weight (%)	52 wk	M	10	0.55	0.61	0.59	0.36*	0.30*
	104 wk	M	10	0.52	0.60	0.55	0.21	0.19*
Pathology - Bilateral changes								
Testes Soft	52 wk	M	20	/	/	2	17	17
	104 wk	M	70	7	7	27	58	59
Reduction in size	52 wk	M	20	/	/	2	16	19
	104 wk	M	70	1	6	19	56	61
DegTub	52 wk	M	20	/	/	2	18	13
	104 wk	M	70	2	2	16	62	67
InhibSperm	52 wk	M	20	/	/	3	17	13
	104 wk	M	70	2	3	16	62	67
InterOed	52 wk	M	20	/	/	3	16	15
	104 wk	M	70	/	/	/	/	/
EPIDIDYMIDES - Bilateral changes								
Reduction in size	52 wk	M	20	/	/	2	4	6
	104 wk	M	70	2	7	18	30	43
OligoSperm	52 wk	M	20	/	/	3	20	18
	104 wk	M	70	2	3	15	62	67
RedTub	52 wk	M	20	/	/	2	2	/
	104 wk	M	70	/	/	6	12	13
EpithAtroph	52 wk	M	20	/	/	/	/	/
	104 wk	M	70	/	/	4	30	26
LUNGS - Foamy alveolar macrophages								
	104 wk	F	70	10	4	17	37	45

DegTub = degeneration of seminiferous tubules; InhibSperm = inhibition of spermatogenesis
InterOed = interstitial oedema; OligoSperm = oligospermia;
RedTub = tubules reduced in size; EpithAtroph = epithelial cell atrophy;
* = significantly different from control ($p \leq 0.05$);

4.2. **1-year feeding study in the dog** (Brunk et al. 1992)

Groups of beagles (6 animals/sex/group) received (95.8%) at dietary levels of 0 - 320 - 1600 or 8000 ppm for 1 year. Satellite groups consisting of 2 males and 2 females were treated analogously at the same dietary levels, but sacrificed after 6 months of treatment. These concentrations were equivalent to a mean daily substance intake (mg/ kg body weight) of 0, 24, 129 and 592 (males) and 0, 21, 115 and 575 (females). In addition, various tissues were taken for residue determinations in view of the lipophilic nature of this part of the study is reported under section 1.4.

Food consumption appeared to be impaired in the highest dose group (8000 ppm); however, no changes in body weight could be observed. Some dogs from the two highest dose groups showed more or less marked non-dose-related deterioration of general health; one male dog from the highest dose group died on day 323 of treatment; an advanced stage of liver fibrosis with nodular change and expansive necroses was histologically evident.
Haematology - Slightly reduced erythrocyte counts were matched by correspondingly slight reductions of haemoglobin concentrations; these findings which were transitory and no longer present at the end of the study were found more frequently at 8000 ppm and occasionally at 1600 ppm.
Clinical chemistry parameters - Feeding at 1600 and 8000 ppm caused a consistent dose-related and marked increase in alkaline phosphatase in both sexes. In addition, an increase in ALAT (GPT) and ASAT (GOT) occurred more frequently at 8000 ppm. The changes in ALAT and ASAT observed at all dose levels after 1-month treatment were very slight in degree and showed no dose-dependency; therefore, a treatment-relationship appears to be unlikely. A slight to medium decrease in cholesterol was also found in the two highest dose groups, but not consistently at all examination times.
Organ weights - At the 6-month sacrifice, the relative liver weights were increased in all treated groups. The dogs killed after 12 months showed increases, except for the 1600 and 8000 ppm groups; in the 8000 ppm group, the absolute weights were also increased. In all cases, the increase in liver weights showed a clear dose-dependency and is therefore considered to be substance-related. In addition, the relative adrenal weight was increased in the middle and highest dose groups.
Pathology - After 6 months of treatment, hypereosinophilic hepatocytes were found in periportal areas in the liver of some animals from all treatment groups. At 8000 ppm, one male dog died of liver failure (jaundice) on day 323. Histologically, an advanced stage of liver fibrosis with nodular change and expansive necroses was evident. Another female dog from this group which survived until the end of the study had developed a more moderate stage of hepatic fibrosis. In the liver of other animals treated at 1600 ppm (one female) and 8000 ppm (four males and one female), interlobular interseptal connective tissue formation could be found. Hypereosinophilic hepatocytes in periportal areas as well as atrophy of the adrenal zona fascicularis occurred sporadically in all treated groups. However, hypereosinophilic hepatocytes as well as atrophy of the adrenal zona fascicularis were not associated with any cell or tissue lesions. For this reason and because of their reversibility, these changes were interpreted as toxicologically not relevant, but considered to be an adaptive phenomenon.

Assessment - Based on these results, the "No Toxic Effect Level" was considered to be approximately 320 ppm, equivalent to a mean daily substance intake of 23.7 and 21.4 mg/kg body weight for the male and female dogs, respectively.

Re-evaluation - However, based on the slight increase in liver weight at 320 ppm at the 6-month interim kill, the "No Toxic Effect Level" can be considered to be slightly lower than 320 ppm.

1-year dog - toxic effects in liver and haematology

Parameter	Duration	Sex	No.	Dose (mg/kg diet) 0	320	1600	8000
Liver weight (%)	6 months	M&F	4	3.29	3.87*	3.97*	4.64*
	12 months	M&F	12	3.37	3.69	4.34*	4.55*
Alkaline phosphatase (U/l)	6 weeks	M&F	16	146	170	277*	358*
	3 months	M&F	16	135	161	261*	396*
	6 months	M&F	16	94	129	220(*)	346*
	9 months	M&F	12	89	120	225	413(*)
	12 months	M&F	12	86	115	217*	418*
Haematology RBC	6 weeks	M&F	16	6.20	6.29	5.93*	5.74*
	3 months	M&F	16	6.50	6.25(*)	5.96(*)	5.79(*)
	6 months	M&F	16	6.63	6.25(*)	5.94(*)	5.80(*)
	9 months	M&F	12	6.66	6.54	6.01*	6.04*
	12 months	M&F	12	6.60	6.49	6.15*	6.12*
Hb	6 weeks	M&F	16	145	146	139	134*
	3 months	M&F	16	152	148(*)	143(*)	138(*)
	6 months	M&F	16	156	149(*)	143(*)	139(*)
	9 months	M&F	12	153	155	145*	145*
	12 months	M&F	12	156	159	147	147
Ht	6 weeks	M&F	16	0.42	0.43	0.41	0.40*
	3 months	M&F	16	0.45	0.44(*)	0.42(*)	0.40(*)
	6 months	M&F	16	0.46	0.44(*)	0.41(*)	0.40(*)
	9 months	M&F	12	0.46	0.45	0.42*	0.43*
	12 months	M&F	12	0.46	0.46	0.43	0.43

RBC = erythrocytes (10^{12}/l; Hb = haemoglobin (g/l); Ht = haematocrit
* = significantly different from the control ($p \leq 0.05$)

Add-on 1-year feeding study in dogs (Stammberger, 1994)

In view of the changes in liver and adrenal gland occurring in all treated groups during the first study a supplementary study was performed in order to establish a clear NOEL for these changes.
(94.2 %) was administered to groups of Beagles (6 animals/sex/group) at dietary levels of 0 - 60 - 160 or 1600 ppm over a period of 1 year. These concentrations were equivalent to a mean daily substance intake (mg/kg body weight) of 0, 4.7, 11.8 and 125 (males) and 0, 4.5, 11.0 and 119 (females). This study included also special endocrinological parameters in order to elucidate more precisely the hormonal status of the adrenal gland and also of the male reproductive organs. In addition, adipose tissues were taken for residue determinations in view of the lipophilic nature of this part of the study is reported under section 1.4.

Food consumption was not impaired in any dosing group, whereas the body weight gains of the females from the high dose group showed a slight to marked decrease. One control male, one low dose

female and two high-dose females had to be killed prematurely, all of them due to poor health condition. These findings could not be attributed to treatment with the test substance.
With a view to the liver as possible target organ the results indicate a consistent distinct increase in ALP in both sexes at all examination times and a slight increase in liver weight in the high dose females. No changes were observed in GOT and GPT activities and histopathology revealed no substance-related changes either.
Haematology revealed a slight, but consistent decrease in erythrocytes and haemoglobin content in the females over the whole study period; a tendency towards this effect was also recognisable in the males at the highest dose (1600 ppm).
All other examinations, including the special measurement of serum testosterone and urinary cortisol, indicated no substance-related changes.
Based on these considerations, the NOEL was established to be 160 ppm (diet), equivalent to a mean daily substance intake of 11.4 mg/kg body weight.

Add-on 1-year dog - toxic effects				Dose (mg/kg diet)			
Parameter	Duration	Sex	No.	0	60	160	1600
Liver weight (%)	12 months	M	5-6	3.48	3.72	3.59	3.73
		F	4-6	3.93	4.04	3.97	4.53*
Alkaline phosphatase (U/l)	6 weeks	M&F	12	144	148	151	247*
	3 months	M&F	12	109	116	117	214*
	6 months	M&F	12	87	97	100	161(m)
	9 months	M&F	12	72	92	87	192*
	12 months	M&F	12	63	63	84(f)	176*
Haematology							
RBC	6 weeks	M&F	12	6.64	6.36	6.62	6.28
	3 months	M&F	12	6.36	6.23	6.26	5.88(f)
	6 months	M&F	12	6.44	6.45	6.41	5.94(f)
	9 months	M&F	12	6.42	6.15	6.48	5.91(f)
	12 months	M&F	12	6.58	6.38	6.54	5.89(f)
Hb	6 weeks	M&F	12	152	148	155	144
	3 months	M&F	12	148	146	146	136(f)
	6 months	M&F	12	150	152	152	139(f)
	9 months	M&F	12	151	147	154	140(f)
	12 months	M&F	12	154	148	155	139(f)
Ht	6 weeks	M&F	12	0.45	0.44	0.45	0.42
	3 months	M&F	12	0.44	0.43	0.43	0.40(f)
	6 months	M&F	12	0.44	0.44	0.44	0.41(f)
	9 months	M&F	12	0.44	0.43	0.44	0.41(f)
	12 months	M&F	12	0.45	0.43	0.45	0.40(f)

RBC = erythrocytes (10^{12}/l; Hb = haemoglobin (g/l);
* = significantly different from the control ($p \leq 0.05$)
(m) = only male value statistically significant;
(f) = only female value statistically significant;
(r) = reticulocytes in females show statistically significant increase

4.3. Combined chronic toxicity and oncogenicity study in mice (Simonnard, 1993)

In a combined chronic toxicity / oncogenicity study, (96.1% purity) was fed to Swiss mice (90 males and 90 females/group) in the diet at concentrations of 0, 400, 3500, or 7000 ppm for two 97 weeks. These concentrations were equivalent to a mean daily substance intake (mg/kg body weight) of 68, 615 and 1271 (males) and 83, 728 and 1481 (females). Twenty mice per sex and group were killed after 52 weeks, in order to evaluate chronic toxicity. Fifty mice per sex and group were scheduled for sacrifice after 97 weeks to evaluate the carcinogenic potential. Further 20 mice per sex and group were scheduled for residue determinations in various tissues at different times in view of the lipophilic nature of ; this part of the study is reported under section 1.4..

Treatment with was generally well tolerated; from week 80 onwards, a slightly higher mortality was observed in males given 7000 ppm and from week 53 a slightly lower (up to 5 %) body weight in the males of the two highest dose groups. The only changes of toxicological significance were an increase in liver weights (up to 25 %) at week 52 and 97 in line with hepatocellular hypertrophy in both sexes at 3500 and 7000 ppm at week 97.

Haematology indicated no impairment of the red blood cell parameters at the different examination times.

Based on these results the NOAEL was considered to 400 ppm, which was equivalent to a mean daily substance intake of 68 and 33 mg/kg body weight in the males and females, respectively.

In addition, showed neither carcinogenic potential nor any effect on the incidence of spontaneously occurring tumours. Moreover, no decrease in latency of tumour appearance was observed.

The non-neoplastic and neoplastic changes in the liver are shown in the following table.

2-year mouse - toxic effects				Dose (mg/ kg diet)			
Parameter	Duration	Sex	No.	0	400	3500	7000
Liver Weight (%)	52 wk	M	10	4.9	4.3	5.7*	6.1*
		F	10	4.9	5.0	6.2*	6.6*
	97 wk	M	26 - 40	5.8	5.3	7.3*	6.7*
		F	24 - 31	5.3	4.9	5.9*	6.6*
Hepatocell. Hypertrophy	52 wk	M	20	/	/	/	/
		F	20	/	/	/	/
	97 wk	M	50	/	/	8	22
		F	50	/	/	1	23
Hepatocell. Adenoma	52 wk	M	20	/	/	1	/
		F	20	/	/	/	/
	97 wk	M	50	8	3	9	8
		F	50	/	1	/	1
Hepatocell. Carcinoma	52 wk	M	20	/	/	1	/
		F	20	/	/	/	/
	97 wk	M	50	5	1	8	7
		F	50	/	/	1	/

* = stat. significantly different from control ($p \leq 0.05$)

4.4. Other routes

A chronic inhalation toxicity study in rats was not conducted, because human exposure to via the inhalation route is unlikely for the following reasons :

The vapour pressure of is very low, i.e. 5.5 x 10^{-6} at 25°C (Grewer, 1988) and thus no relevant inhalation exposure of vapour is possible.
is an oily liquid; therefore the formation of inhalable fine dust is not possible.

5. MUTAGENICITY AND RELATED EFFECTS

5.1. in vitro mutagenicity testing

Gene mutation

Prokaryotes (Ames-Test) (Müller, 1987)

(93.4%), dissolved in DMSO, was tested in Salmonella typhimurium TA 98, TA 100, TA 1535, and TA 1537 and in Escherichia coli WP2 uvrA for the potential to induce reverse gene mutations. The concentrations used ranged from 4 to 10000 µg/plate in the 1st experiment and from 4 to 10000 µg/plate in the 2nd experiment. At concentrations equal to or exceeding 2500 µg/plate, precipitation of the test material was noted. No mutagenic activity was noted either in the presence or in the absence of a rat liver derived activation system.

Mammalian cells - HGPRT-test in Chinese hamster V-79 cells (Müller, 1988)

In the in vitro HGPRT-test using the Chinese hamster cell line V-79, no increased rate of mutation was detected either in the presence or in the absence of a rat liver S9 microsomal fraction in two independent experiments. The concentrations of (96.8%), dissolved in DMSO, tested ranged from 250 to 1000 µg/ml and were limited by the solubility of the test substance above 1000 µg/ml.

Chromosomal aberration

Cultured human lymphocytes (Heidemann, 1988)

(96.8%) was dissolved in DMSO and tested in concentrations of 6.0, 60 and 160 µg/ml for its potential to induce structural chromosome aberrations in human lymphocytes in vitro. Preparation of chromosomes was done 24 h (all doses), and 48 h (highest dose) after the start of treatment (duration 4 h). In each experimental group two parallel cultures were used and 100 metaphases were scored per culture. Treatment of the cells with highest concentrations reduced the mitotic index at fixation interval 24 h in both the presence and absence of metabolic activation (liver S-9 mix) and 48 h with S9 mix. In this test induced no biologically relevant increases in aberrant cells in contrast to the positive reference substances used.

DNA-pertubation / damage

Prokaryotes - Rec assay in B. subtilis (Ohtsuka, 1990)

(93.2%) was dissolved in DMSO and tested for differential toxicity in recombination repair proficient and repair-deficient strains of Bacillus subtilis (H17 and M45) in the absence and presence of an activation system at 5 doses between of 625 and 10000 µg/disk. did not produce a zone of killing up to 10000 µg/disk in either strain and was negative in the assay in contrast to the reference substances. was considered to have no potential of DNA damage under the conditions of this test.

Eukaryotes - Mitotic gene conversion in Saccharomyces cerevisiae (strain D4) (Forster, 1988)

(96.8%) was dissolved in ethanol and tested in 6 concentrations ranging from 39 to 1250 µg/ml with and without metabolic activation for the induction of mitotic gene conversion in Saccharomyces cerevisiae (strain D4) in two independent experiments. The maximum dose level was the highest concentration which could be achieved in the assay medium without exceeding acceptable solvent concentrations. did not induce three-fold increases in the frequency of mitotic gene conversion and was not toxic to the test organism at any dose level in contrast to the positive reference substances used.

Mammalian cells - UDS-test in the mammalian cell line A549 (Kramer & Müller 1988)

(96.8%) was examined in the in vitro unscheduled DNA synthesis test (UDS-test) in the mammalian cell line A549 by excision repair in cells in culture. The test was performed in the presence and absence of metabolic activation (rat liver S-9 fraction). Two independent experiments with 7 concentration levels (range 1 to 2000 µg/ml) were carried out using DMSO as solvent. No relevant reproducible increase in unscheduled DNA synthesis was observed in any test with in contrast to the positive reference substances used in this test.

5.2 in vivo mutagenicity testing

Micronucleus test in mice (Müller, 1988)

In the mouse micronucleus test, (96.8%) was dissolved in sesame oil and administered orally to groups of 5 male and 5 female NMRI mice at a single dose of 1250, 2500 or 5000 mg/kg body weight. Evaluation of bone marrow smears (scoring of 1000 polychromatic erythrocytes per animal) obtained 24, 48 and 72 hours after dosing with did not demonstrate any increase in the incidence of micronuclei in contrast to the positive reference substance endoxan.

Bone marrow chromosome aberration assay in the Chinese hamster (Völkner, 1988)

(96.8%) was dissolved in paraffin oil and administered orally to groups of 5 male and 5 female Chinese hamsters at a single dose of 150, 500 or 1500 mg/kg body weight. The animals from the highest dose exhibited clinical signs in the form of apathy indicating that the maximum dose suitable for the test system had been reached. From each animal 50 well spread metaphases were scored for gaps, breaks, fragments, deletions, exchanges and chromosomal disintegrations. Evaluation of bone

marrow smears obtained 24, 48 and 72 hours after dosing with did not demonstrate any increase in the chromosome aberration frequency in contrast to the positive reference substance cyclophosphamide.

6. REPRODUCTION TOXICITY

6.1 EMBRYOTOXICITY AND TERATOGENICITY

Rat - oral route (Baeder, 1989)

(94.9%) was suspended in starch mucilage and administered in a limit test orally by gavage once daily from days 6 to day 16 of gestation to groups of 20 female Wistar rats at a dose level of 0 (vehicle control) or 1000 mg/kg body weight. The dams were killed and delivered by caesarean section on day 20 of gestation. The foetuses were then examined morphologically for developmental disturbances. Testing showed that treatment with had no harmful effect on the general condition of the dams or on the intrauterine development of the conceptuses. The morphological examination of the foetuses for stage of development, external anomalies and anomalies of the internal organs and skeleton provided no evidence of an embryotoxic or teratogenic potential of
Thus, the No Observed Effect Level in rats for maternal as well as developmental effects was 1000 mg kg body weight.

Rabbit - oral route (Baeder, 1988, Albrecht & Baeder 1990)

1st study: (94.9%) was mixed with starch mucilage and administered in a limit test orally by gavage once daily from days 6 to day 18 of gravidity to groups of 15 female Himalayan rabbits at a dose level of 0 (vehicle control) or 1000 mg/kg body weight. The dams were killed and delivered by caesarean section on day 29 of gravidity. The foetuses were kept for 24 hours in an incubator as a viability check and then examined morphologically for developmental disturbances.
Testing showed that treatment with caused a slight reduction of food consumption of the dams during the treatment and an increased incidence of intrauterine deaths. The live foetuses at delivery were normally developed in outward appearance and showed no impairment of viability during the first 24 hours. Morphological examination indicated a slight embryotoxic effect in the form of increased incidences of a 13th rib in the treated group, but there was no evidence for any teratogenic potential of

The No Observed Effect Level in rabbits for maternal as well as developmental effects was considered to be less than 1000 mg/kg body weight.

Add-on study: As a follow up of above reported Limit test with a dose of 1000 mg/kg body weight, (94.9%) was mixed with starch mucilage and administered in a orally by gavage once daily from days 6 to day 18 of gravidity to groups of 15 female Himalayan rabbits at a dose level of 0 (vehicle control), 100 or 300 mg/kg body weight. The dams were killed and delivered by caesarean section on day 29 of gravidity. The foetuses were kept for 24 hours in an incubator as a viability check and then examined morphologically for developmental disturbances.
Testing showed that treatment with at doses up to and including 300 mg/kg body weight had no harmful effect on the general condition of the dams or on the intrauterine development of the conceptuses. The viability of the foetuses during the first 24 hours in the incubator also remained unaffected. The morphological examination of the foetuses for stage of development, external anomalies

and anomalies of the internal organs and skeleton provided no evidence of an embryotoxic or teratogenic potential of
Thus, the No Observed Effect Level in rabbits for maternal as well as developmental effects was 300 mg/kg body weight.

Rat - embryotoxicity and postnatal development (Albrecht & Baeder 1991)

(93.2%) was suspended in starch mucilage and administered in a limit test orally by gavage once daily from days 6 to day 16 of gestation to groups of 20 female Wistar rats at a dose level of 0 (vehicle control) or 1000 mg/kg body weight. The dams were to deliver normally and rear their offspring for 21 days. During the rearing period the physical development and viability of the offspring were examined. After this all of the pups were subjected to function tests, and one male and female pup per litter were also subjected to behaviour and activity tests. The study was terminated by autopsy of dams and offspring.
Testing showed that treatment with did not impair the general condition of the dams, interfere with the course of gravidity and delivery, or cause any disturbance of the intrauterine or post-natal development of the offspring.
The No Observed Effect Level for maternal toxicity, embryonic/foetal and post-natal toxicity in this study was 1000 mg/kg body weight.

6.2. TWO-GENERATION REPRODUCTION STUDY IN THE RAT

Preliminary study (Dotti et al. 1993)

In a preliminary study to the two-generation reproduction study (96.1%) was administered at dietary concentrations of 0, 400, 2000 and 10000 ppm to groups of 10 male and 10 female Wistar rats during a 3-week pre-pairing period and throughout the pairing (maximum of 15 days), gestation and lactation periods. After weaning (day 21 post partum), the parents and F1 pups which were not selected for organ weight analysis were reared for a further week on the respective test diet. At 2000 and 10000 ppm, there was a reduction in food consumption in the females during the lactation period and a reduction in the mean number of implantation sites and pups per dam. At 10000 ppm, retardation of body weight gain was noted in the parents as well as in the pups; additionally, the food consumption of the pups was reduced from days 21 - 28 post partum. The parent males of this group showed markedly reduced weight of the testes (30%). Based on these results dosages of 200, 1000 and 5000 ppm (diet) were chosen for the main study.

			Dose (mg/ kg diet)			
Parameter	**Sex**	**No.**	**0**	**400**	**2000**	**10000**
Weight of male reproductive organs (%)						
Testes	M	10	0.97	0.94	0.93	0.68*
Litters	F	10	10	10	10	9
Implantations per dam	F	10	12.4	12.1	9.9	9.2*

Two-generation reproduction study in the rat (Dotti et al. 1993$_3$).

Study design : In a two-generation reproduction study (96.1%) was fed in the diet to groups of 25 male and 25 female rats in concentrations of 0 - 200 - 1000 or 5000/2000 ppm; due to reduced male fertility at 5000 ppm, this dose level was reduced to 2000 ppm at the beginning of the preparing period of the F1 generation. The animals received the test material over a period of 70 days prior to mating (F1A) and throughout gestation and lactation. The P generation were mated again to produce the F1B generation. During weaning of the F1B generation, pups were selected to deliver the F2A and F2B generations. Diet containing was fed to all animals of all generations.
In addition to this study design the following special tests were performed: After weaning of the F1 pups, 15 males and 15 females of the P generation in the control and 5000 ppm groups were selected for a "cross foster" pairing, i.e. 5000 ppm males were paired with control females and vice-versa; during this phase both groups received control diet. From the F1 parent males, blood samples were collected prior to necropsy for the determination testosterone and progesterone in the plasma.
In addition, deep frozen adipose tissue and plasma samples were preserved from selected parents and pups from both generations for residue examinations. From these plasma samples, testosterone and progesterone levels of the parent males of the P and also of the F1 generation (for verification) were determined. The results of the residue examinations in adipose tissue is reported under section 1.4.

Results :
General parental toxicity: Slight general toxicity was established from 2000 ppm onwards in the F1 parents and also in the 5000 ppm females (during lactation) of the P generation in the form of reduced food consumption. Clinical signs related to treatment were not observed at any stage of the study. With regard to parameters related to reproduction toxicity, the following changes were noted :
Male and female fertility: At 5000 ppm (P generation) the number of pregnant females, the mean number of implantation sites per dam and the litter size were markedly reduced. The "cross foster" pairing indicated that this effect was due to reduced male fertility. This finding was confirmed by the reduced testes weight (18%) and by macroscopy (testes flaccid or reduced size in 16% of the males). Additionally, histopathology revealed atrophy of seminiferous tubules in the testes with concomitant reduction in spermatozoa and the presence of exfoliated seminiferous tubular epithelial cells in the epididymides.
At 1000 and 2000 ppm, increased plasma levels of progesterone were noted in the F1 males. However, in the absence of any corresponding change in the testosterone levels and taking into consideration that no impairment of male fertility occurred up to 2000 ppm, no toxicological relevance was assigned to this change. This judgement may be considered to be supported by the supplementary (re)examination of the deep frozen plasma samples (Burri, 1995 : Selected males of the P generation with testicular lesions showed no changes in testosterone and progesterone and the verifying examinations of selected F1 males could not confirm the increase in progesterone as observed at the first measurement. Therefore, it can be concluded that no endrocrinological mechanism is involved in the impairment of male fertility.
Progeny : At 5000 ppm a slight impairment in body weight development was noted in the F1 pups during the lactation period; this effect must be seen in connection with the reduced food consumption of the dams. At 2000 ppm a slight increase of the number of dead pups at first litter check was noted in the F2B litters.

The No Adverse Observable Effect Level for the parent animals, for the reproduction data and for the progeny data was considered to be 1000 ppm, equivalent to a mean daily substance intake of 69.2 and 96.3 mg/kg body weight for the males and females, respectively.

The changes in male reproduction parameters are summarised in the table below:

P-Generation	Diet concentration (ppm)				
Parameter	No.	0	200	1000	5000
Testes weight (%)	25	0.85	0.92	0.91	0.70*
Pathology					
flaccid or reduced in size	25	/	/	/	4
SemTubAtroph	25	/	/	1	12
Epith vacuolation	25	/	/	/	8
Epididymides - Pathology					
ReducSperm	23 - 24	/	/	/	10
EpithAtroph	23 - 24	/	/	3	19
Male fertility - pregnant dams (% mated)					
Standard experiment	25	100	100	96	36*
HD males & control females	15	100			53*
Control males & HD females	15	100			100
Testosterone/ progesterone Burri 1995	4-5	1.4 / 7.8	1.4 / 5.0	3.3 / 7.8	3.8 / 4.5
F1-Generation	Diet concentration (ppm)				
Parameter	No.	0	200	1000	2000
Testes weight (%)	25		NS	NS	NS
SemTubAtroph	25	1	ND	ND	/
Epididymides					
ReducSperm	25	1	ND	ND	/
EpithAtroph	25	2	ND	ND	1
Testosterone (ng/ml)	25	0.95	0.9	1.16	0.78
verification by Burri 1995	3-5	1.45	ND	ND	ND
Progesterone (ng/ml)	25	0.18	0.28	0.74*	0.97*
verification by Burri 1995	3-5	2.5	3.1	2.5	3.0

NS = not significantly different from control; * = stat. significant at $p \leq 0.05$;
/ = no finding; ND = not determined; HD = highest dose (5000 ppm)
SemTubAtroph = atrophy of seminiferous tubules;
ReducSperm = reduction in spermatozoa;
EpithAtroph = epithelial cell atrophy

7. NEUROTOXICITY STUDIES

Acute delayed neurotoxicity in adult hens (Ebert, 1990)

(96.8 %), as original, was administered twice orally at the limit dose of 5000 mg/kg body weight to 12 White Leghorn hens, with an interval of 21 days between each application. A negative control (sesame oil, 4.6 ml/kg body weight) and a positive control (TOCP, 500 mg/kg body weight), each composed of 6 hens, were also included in the study. The neurotoxicity study was preceded by an acute oral toxicity study of the test substance (LD_{50}).
After treatment with the test substance no clinical signs of intoxication were observed and all hens survived until the end of the study. No clinical signs of delayed neurotoxicity in the form of ataxia could be established. Histopathological examination of brain, spinal cord and peripheral nerves indicated no pathomorphological lesions. In contrast, the hens in the positive control group (TOCP) showed the typical neurotoxic effects produced by this reference substance in the form of prolonged delayed-onset severe ataxia or, in some of the animals, paralysis, together with pathomorphological lesions especially in the form of damage to myelinised nerve fibres. These lesions were strongly marked in the substantia alba of all segments of the spinal cord, and less pronounced in the tractus spinocerebellaris of the medulla oblongata; microscopic examination showed them to be axonal swellings. Based on these results was considered to cause no Organophosporus Induced Delayed Neurotoxicity (OPIDN) at the maximum recommended dose level of 5000 mg/kg body weight.

8. SUPPLEMENTARY STUDIES

Separate mechanistic studies to clarify effects reported in toxicity studies were not conducted. Where necessary, such examinations formed part of the studies concerned and were reported in the study reports or as supplements to the reports.

9. MEDICAL DATA

Medical surveillance of manufacturing plant personnel
is a newly developed chemical. Workers and technical staff involved in the process of experimental synthesis or formulation were exposed to very low levels. These persons were subjected to medical examinations in intervals of 1 to 2 years. These examinations comprise an anamnesis, questionnaires on possible adverse health effects related to the workplace, examination of general health status ,and laboratory examinations such as serum biochemistry (GOT, GPT, γ-GT, creatinine), urinalysis, and extended haematology including thrombocytes and respiratory function.

Direct observation, e.g. clinical cases and poisoning incidents
We have received no reports of adverse effects and /or poisoning under workplace conditions.

Health records from industry and agriculture
No substance-related changes have been indicated by clinical or laboratory examinations, and no adverse effects on health have been recorded among industrial workers. We have received no reports of adverse effects on health caused by poisoning under conditions of experimental agricultural* use.
* since 1995 has been registered in Japan for use as an insecticide in tea, rice, etc.

Sensitisation/allergenicity observations
No dermal allergenic reactions were detected until now.

Expected effects of poisoning
The very low acute toxic potential and the toxicological profile of make it unlikely that accidental poisoning with the substance will occur. However, in view of the toxicological profile observed in acute and short-term toxicity studies, suicidal intake of may possibly result in non-specific signs similar to those observed in the acute animal studies and impairment of the red blood cell and the liver function, which proved to be completely reversible within 4 weeks.

Proposed first aid measures
First aid measures in the case of suicidal intake of should consist of standard hygienic measures, i.e. decontamination and symptomatic treatment of non-specific symptoms. In addition, it is advisable to monitor the red blood cell and liver functions.

10. SUMMARY OF MAMMALIAN TOXICOLOGY AND CONCLUSIONS

10.1. SUMMARY OF MAMMALIAN TOXICOLOGY AND METABOLISM

Absorption, distribution, excretion and metabolism

Data on absorption, distribution and excretion were obtained from rats after single and repeated oral application of ^{14}C-labelled at doses ranging form 10 to 500 mg/ kg body weight. Normally about 90% of the applied radioactivity was excreted via faeces, mostly during the first day after dosing. The predominant portion (> 90%) was excreted via faeces and only 1 to 3.5% via urine, with higher values among the male rats. Up to 4% of the administered amount was still present in the organs after 7 or 28 days, with higher values in the female rats. Excretion in most cases was biphasic, with mean half-lives of 7 and 50 hours, the times for faeces and urine being about the same.

Oral and dermal absorption : All kinetics and metabolism studies indicate a low rate of oral absorption. A special absorption and biliary excretion study proved that biliary excretion plays a relevant role (Büttner 1992); however, the absorption rate determined in this study (about 5 %) must be considered to be of very limited value, because the experiment was performed with narcotised rats, the very limited physiological activity of which resulted in artificially low absorption. A highly specific situation of this kind may present major problems and uncertainties when it comes to estimating the biliary excretion rate of absorbed material, particularly in studies where the amounts of the compound incorporated in the organ and tissues are determined a relatively long time after oral administration. Based on these considerations and with a view to an assessment of human health risk resulting from prolonged low-dose exposure, the study of Kellner et al. 1993, appears to be the most appropriate for estimation of gastro-intestinal absorption : Based on radioactivity measurements in urine and tissues/organs after repeated oral application of low (10 mg/kg) doses determined 4 hours after the last dosing, the minimum oral absorption rates (tissue excl. gastro-intestinal tract plus urine) were estimated to be 13.2 and 12.4 % in the female and male rat, respectively. The maximum dermal absorption of the form of a representative emulsifiable concentration formulation was determined to be 12.25 % at the lowest concentration (0.001 mg / cm^2) and after the longest exposure time (24 hours).
Conclusion : In summary, it is concluded that there is no relevant difference between oral and dermal absorption which considered to be 12.5 % after low dose exposure.

The main component in faeces is , making up 60 to 80% of the applied amount. Up to 10% of the applied amount are present in the form of the de-ethylated metabolite The other (unknown) metabolites in faeces are in each case considerably less than 10%. In urine

are found in free and conjugated (sulphate) form. However, in view of the small amounts excreted via urine and their ready solubility in water, they are of no significance for the overall residue pattern. In general it should be noted that, if the applied amount is taken as the reference magnitude, is a substance which metabolises only to a very low extent. However, if the absorbed portion is taken into account, it will be seen that this is almost completely metabolised.

Based on a study in dairy cows a transfer of into the milk fat took place at concentrations slightly higher as compared with the body fat. However, due to a fat content of about 3 % in the milk, the concentration of in the milk must be considered as very low as indicated by BCF values of 0.03. In addition, the plateau residue level in milk (fat) was reached within a few days and declined rapidly, i.e. after 3 days no residues could be detected. In a study in lactating goats was applied for three consecutive days. Only small amounts were excreted in urine (0.8%) and milk (1.3%). Two hours after the last dosing the highest ^{14}C-levels were found in the liver (76 ppm) and at considerably lower levels in milk (2.9 ppm), kidneys (2.4 ppm), fat (1.3 ppm) and muscle (0.7 ppm). In the other organs and in the milk, only parent compound was detected.

has a high partition coefficient for octanol/water (log P_{ow}) of 8.2. For this reason it had been expected to accumulate in fat, and a series of studies and residue analyses in connection with toxicity studies in rat, mouse and dog were conducted to determine the bioconcentration factor (BCF). The BCF is defined as the quotient of the test substance concentration in fat and administered diet. Considerably high residue concentrations of were measured in adipose tissue at all examination times. The BCF values derived from chronic toxicity studies in different species (rat, mouse, dog) were comparable and ranged from 3 to 5. The residues in fat were eliminated rapidly ($T_{1/2}$ = 4 - 8 days) after single dosing, but considerably more slowly ($T_{1/2}$ = 13 - 132 days) after repeated dosing. Elimination half-lives of 39 - 47 days were calculated in a chronic rat feeding study (5 mg/kg diet). In the other organs and tissues only very low residue levels were found, resulting in BCF values of much less than 0.1 (liver, kidneys, testes) and less than 0.01 (brain).

Conclusion: As a highly lipophilic substance, exhibits a marked, but not unlimited, tendency to accumulate in fat. However, an accumulation in the food chain appears unlikely, since the BCF values for animal-derived food will be less than 1, if the fat content does not exceed 20 to 30 %. During storage in a compartment with low metabolic activity such as adipose tissue, cannot cause harmful effects. After remobilisation from the fat, is rapidly metabolised in the transportation channels and liver to more hydrophilic and readily excretable substances.

General Toxicological Properties

Acute toxicity, local tolerance and sensitisation : Based on the data for acute oral, dermal and inhalation toxicity, must be considered as a chemical of low acute toxicity. The substance proved to be non-irritating to the skin and eye and showed no allergenic potential in the standard tests by the methods of Magnusson & Kligman and Buehler, or in a photosensitisation test. In view of these toxicological properties, the risk of accidental poisoning must be considered as negligible. Repeated dermal and oral exposure causes no increase in the acute toxic potential and single exposure resulted in no

irreversible damage to health. Based on this toxicological profile, is not subject to labelling requirements as defined in EEC directive 93/21/EEC.

The data of these studies are summarised in the table below:

acute toxicity	species	LD50 mg kg^{-1}
oral	rat	> 5000
oral	mouse	> 5000
dermal	rat	> 5000
dermal	rabbit	> 4000
inhalation	rat	>6.61 mg/L air *
intraperitoneal	rat	approx. 1000
skin and eye irritation	rabbit	not irritating
sensitisation (GPMT & Buehler)	guinea pig	not sensitising
photo sensitisation	guinea pig	not sensitising

* = mg/L air; highest applicable concentration for technical reasons

Repeated-dose, subchronic and chronic toxicological profile : Repeated-dose (30-day) and subchronic (90-day) studies in all dogs, rats and mice indicated the liver and the red blood cells as the target organs for toxicity. In addition, the testes proved to be a further target organ, though only in the rat.

Changes in liver : Repeated-dose, subchronic and chronic toxicity studies in all dogs, rats and mice indicated the liver as the main target organ for toxicity. The dog proved to be the most sensitive species. Rat and mouse : In repeated-dose and subchronic studies the toxicological profile was characterised by moderately increased liver weights at 10000 ppm without any clinico-chemical or histological correlates of tissue damage. This effect proved to be fully reversible after 2 - 4 weeks of recovery. After chronic (1-yr and 2-yr) exposure, the increase in liver weight was already recognisable from 2000 ppm and 3500 ppm onwards in rats and mice, respectively, and cellular hypertrophy was also observed. These findings are indicative of an adaptive rather than a toxic response of the liver. The NOEL for hepatic changes is considered to be 400 ppm, equivalent to a mean daily test substance intake of 20 and 68 mg/kg body weight for the rat and mouse, respectively.
Dog : In contrast to rat and mouse, the hepatic changes found in the dog consisted in increased liver weights together with increased serum levels of alkaline phosphatase from 1600 ppm onwards and of GOT and GPT at higher doses; in addition, histopathology identified an advanced stage of fibrosis with nodular change and expansive necroses and interlobular interseptal connective tissue formation at 8000 ppm after chronic exposure; the latter finding was also observed in one female at 1600 ppm, which represents the effective dose for hepatotoxicity. First signs of an impairment of the hepatic function were already recognisable at the 320 ppm exposure level in the form of increased liver weights and alkaline phosphatase after 3 and 6 months of exposure. Based on the chronic (1-yr) supplementary study, the NOEL for hepatic changes is considered to be 160 ppm, equivalent to a mean daily substance intake of 11.4 mg/kg body weight.

Changes in haematology : Dog : Based on the repeated-dose, subchronic and chronic toxicity studies, treatment with at 1600 and 8000 ppm may have caused marginal anaemia in both sexes as indicated by consistent decreases in erythrocytes, haemoglobin and/or haematocrit values at the

majority of the different examination times. These changes, however, are so small in degree, i.e. within the normal biological range, that a substance-dependency can only be derived from the consistency of these minimal changes or trends in all of the different studies. Therefore, a substance-dependency appears to be very unlikely and more a matter of speculation than sound toxicological judgement in view of the isolated changes in the males from the 320 ppm group at months 3 and 6. For this reason, the NOEL for haematological findings is considered to be 320 ppm, equivalent to a mean daily substance intake of 21 mg/kg body weight. Rat and mouse : In the rat, marginal decreases in red blood cell parameters were only observed in the subchronic study among the males from the 10000 ppm group at week 13 and in the chronic study among the females from the 20000 ppm group at week 26. In the subchronic mouse study, a slight decrease in erythrocytes, haemoglobin and haematocrit values and a marginal increase in reticulocytes was observed in the males at 10000 ppm. In the chronic study, a marginal decrease in haemoglobin, but without any dose-relationship, and corresponding decreases in erythrocytes and haematocrit were found among the females from the 3500 and 7000 ppm groups at week 13 only. This finding is considered to be incidental and related to the high control value. In summary, it cannot be ruled out that the red blood cell may also be a target at extremely high doses (10000 ppm) in the male rat and mouse.

Rat male reproductive organs : As in the repeated-dose and subchronic toxicity studies no effects upon the male reproductive organ were found in dogs and mice. In the rat only, there was an increase in pathological changes in the testes and epididymides after 12 and 24 months treatment; such changes were not seen in the 4-wk and 13-wk rat studies at the end of the treatment. These changes consisted in an increase in soft consistency and reduction in size of testes and epididymides associated histologically with degeneration of seminiferous tubules and inhibition of spermatogenesis in testes and oligospermia and small tubules in the epididymides from 2000 ppm onwards (about 100 mg/kg/day), which represents the toxic effective threshold dose for testicular toxicity; at 10000 and 20000 ppm, there was also a decrease in testicular weight.

Summary of adverse effects : The adverse effects relevant for determination of the NOAEL in the different short-term and chronic toxicity studies are summarised in the following table :

type of study	NOAEL ppm	NOAEL mg/kg/d	adverse effects at high dose levels
4-wk feeding rat	2000	(198)	increase in liver weight
4-wk feeding mouse	2000	(472)	slight liver toxicity (weight)
4-wk feeding dog	320	(19)	liver toxicity (weight, enzymes), slight anaemia,
4-wk dermal rat	-	(1000)	-
13-wk feeding rat	2000	(168)	slight liver toxicity (weight), slight anaemia
13-wk feeding mouse	2000	(338)	liver toxicity (weight), slight anaemia
13-wk feeding dog	> 320	(23)	liver toxicity (weight, enzymes), slight anaemia,
2-yr feeding rat	400	(20)	slight liver toxicity (weight); testicular toxicity
2-yr feeding mouse	400	(68)	liver toxicity (weight, histology)
1-yr feeding dog	160	(11)	liver toxicity (weight, enzymes), marginal anaemia,

Based on the repeated-dose to chronic toxicological profile, is not subject to labelling requirements as defined in EEC Directive 93/21/EEC.

Specific toxicological properties

Carcinogenicity, mutagenicity and developmental toxicity / fertility : The carcinogenic potential of was investigated in two life-span studies with rats and mice. Both studies included extremely high dosing levels of 7000 ppm and 20000 ppm in mice and rats, respectively reaching or exceeding the limit dose of 1000 mg/kg body weight per day for such studies. Neither study indicated a carcinogenic potential of . The genotoxic potential was adequately evaluated in a test battery including gene mutation, chromosome aberration and DNA damage /repair tests. None of the tests yielded indications of a genotoxic potential. In a two-generation study in rats proved to be slightly toxic for the parental generations as indicated by slightly reduced food consumption at dietary concentrations of 5000/2000 ppm. At 5000 ppm about 350 mg/kg b.w.) caused reproductive toxicity in the form of an impairment of male fertility together with testicular lesions; this effect could not more detected after dose reduction to 2000 ppm (140 mg/kg b.w.). Based on special hormonal examinations and histological expert judgement (Weinbauer 1994), this specific organ toxicity is more likely to have been caused by a cytotoxic basic mechanism on the Sertoli cells than by hormonal imbalance. No special toxicity to the offspring was observed during the lactation period. No developmental toxicity was observed in rats and rabbits up to and including doses which proved to be toxic to the dams. The data of the studies on carcinogenicity, mutagenicity and reproduction / developmental toxicity in the following table :

type of study	NOAEL ppm	NOAEL mg/kg/d	adverse effects at higher dose levels
oncogenicity rat	20000	1000	not carcinogenic
oncogenicity mouse	7000	>1000	not carcinogenic
Ames test			negative
Rec assay B. subtilis			negative
Mitotic gene conversion in S. cer. D4			negative
HGPRT V79 cells			negative
Chromosomal aberration human lymphocytess			negative
UDS test in human A549 cells			negative
Micronucleus test in mice			negative
2-generation rat	1000	69M 96F	Parents: decreased food intake; testicular toxicity and impairment of fertility Progeny: slightly reduced body weight during lactation
embryotoxicity rat	dam /pup :	1000	-
embryotoxicity rabbit	dam /pup :	300	dam: reduced food intake Embryo/foetus : intrauterine death
post-natal rat	dam /pup :	1000	-

Based on the studies on specific toxicological properties - carcinogenicity, mutagenicity, developmental toxicity - is not subject to labelling requirements as defined in EEC Directive.
With a view to the impairment of male fertility together with testicular lesions in rats at high doses (about 374 mg/kg b.w.), there is no sufficient evidence to provide a strong presumption that human exposure to may result in impaired male fertility. Although testicular lesions was not observed

in the chronic dog and mouse studies, it cannot be definitively excluded that may cause concern for human fertility. For this reason, should be preventively classified as **"Harmful (Xn)" and labelled with risk phrase "R62: Possible risk of impaired fertility"** according to the principles of Directive 93/21/EEC.

10.2. CONCLUSIONS

Tolerable Daily Exposure for consumer (TDE)

Since health risks to consumers may be presented by chronic exposure, the proposal of the tolerable exposure to is based on chronic feeding studies conducted in dogs, rats and mice. The following NOAELs were obtained in these studies:

	NOAEL	
type of chronic study	ppm diet	mg/kg b.w./day
chronic (1-yr) oral toxicity in dogs	160	11
chronic (2-year)oral toxicity in mice	400	68
chronic (2-yr) oral toxicity in rats	400	20
two-generation reproduction in rats	1000	69

The lowest NOAEL values of 20 and 11 mg/kg/day were established in the chronic rat and dog study, respectively.
Taking into account the toxicological profile (liver and haematotoxicity) observed in these studies, a safety factor of 100 would be sufficiently conservative in case of the dog study resulting in an oral TDE of 0.11 mg/kg body weight / day. This TDE is considered to be as most appropriate as the toxicological profile corresponds closely to that observed also in the other species (mouse, rat) so that a high predictive value for human health risk must be expected. In the case of the rat reproduction study a higher safety factor of 250-fold is considered to be appropriate taking into account the specific toxic effects on male fertility and would result in an oral TDE of 0.28 mg/kg body weight per day. However, the predictive value of this study appears to be limited as no testicular toxicity was seen in the chronic dog and mouse studies.
Based on these considerations and taking into account an oral and dermal absorption of about 12.5 % and an inhalational absorption of 100 % the following TDE values are proposed:

$TDE_{oral/dermal}$: ***0.11 mg/kg body weight per day***
$TDE_{inhalational}$: ***0.014 mg/kg body weight per day***
(0.98 mg / 70 kg person)
: ***49 µg/m³ air****

* calculation basis : body weight human : 70 kg; respiratory volume : 20 m³ per 24 hours; average of resting (16hrs) and light activities (8hrs) rates;

Acceptable Operator Exposure Level (AOEL)

Since health risks to operators relates to short-term rather than to chronic exposure, the NOAELs derived from short-term and developmental toxicity testing and the relevant parts of the multigeneration test (F_0 and F_1, but not F_2 generation) should be taken into account for the purposes of establishing an AOEL. In the case of the following NOAELs were obtained in these studies following oral exposure:

	NOAEL	
type of short-term study	ppm diet	mg /kg b.w./day
1-yr feeding dog	160	11
13-wk feeding dog*	>320	>23
13-wk feeding rat	2000	168
13-wk feeding mouse	2000	338
reproduction in rats (F_2 and F_1)	1000	69
developmental toxicity rat	-	1000
developmental toxicity rabbit	-	300
4-wk dermal toxicity rat	-	1000

*based on the toxicological profile derived from different dog studies, there is no indication of any cumulative toxicity; therefore the NOEL established in the 1-year study is considered to be appropriate for estimation of the AOEL resulting from short-term exposure

The lowest NOAEL values of 11 and 69 mg/kg/day were established in the short-term dog and rat reproduction study, respectively. Based on the considerations given in connection with the proposal of the TDE values, the dog study is considered to be most suitable for establishing an AOEL value.

Taking into consideration the relatively short-term exposure of operators a safety factor of 25 is considered to be sufficiently conservative for assessment of operator/worker risk based on the toxicological effects (liver and haematotoxicity) observed in the dog as the most sensitive species.

Based on these considerations and taking into account an oral and dermal absorption of about 12.5 % and an inhalational absorption of 100 % the following TDE values are proposed:

$AOEL_{oral/dermal}$: ***0.44 mg/kg body weigt per day***
$AOEL_{inhalational}$: ***0.055 mg/kg body weight per day***
(3.85 mg / 70 kg person)
: ***385 µg/m³ air****

* calculation basis : body weight worker : 70 kg; respiratory volume : 10 m³ per 6 hours; (light work;

10.3. Proposal for classification and labelling

Based on the studies on general and specific toxicological properties - carcinogenicity, mutagenicity, developmental toxicity - is not subject to labelling requirements as defined in the EEC Directive.

With a view to the impairment of male fertility together with testicular lesions in the rat at high doses (about 374 mg/kg b.w.), there is no sufficient evidence to provide a strong presumption that human exposure to may result in impaired male fertility. Although testicular lesions were not observed in the chronic dog and mouse studies, it cannot definitively excluded that may cause concern for human fertility.

According to Directive 93/21/EEC of April 27, 1993, should therefore be preventively classified as a "category 3" reproductive toxicant

HARMFUL (X_n)

and labelled with the following risk phrase:

"R62: Possible risk of impaired fertility"

With respect to the bioaccumulation potential in adipose tissue as indicated by BCF values ranging from 3 to 5, it must be stressed from the toxicological viewpoint that this property was not connected with any cumulative toxicity or specific reproduction toxicity to the offspring during lactation.
In addition, the maximum plateau concentrations were reached within the exposure periods of the studies used for assessment of human health risk.
Therefore, no special toxicological considerations or additional labelling proposals resulting from this specific property of are considered to be appropriate.

Date of Evaluation: June 1995
Dr. Ebe/

Hoechst Schering AgrEvo GmbH
Toxicology Frankfurt

(Dr. K.-H. Leist) (Dr. E. Ebert)

11. REFERENCES

Albrecht M. & Baeder Ch. (1990) : : Testing for embryotoxicity in the Himalayan rabbit after oral administration; Hoechst Report

Albrecht M. & Baeder Ch. (1991) : :Testing for embryotoxicity and effects on post-natal development in Wistar rats after oral administration (limit test); Hoechst Report

Baeder Ch. (1988) : :Testing for embryotoxicity in the Himalayan rabbit after oral administration (limit test); Hoechst Report

Baeder Ch. (1989) : Testing for embryotoxicity in the Wistar rat after oral administration (limit test); Hoechst Report

Brunk R. (1988) : :Testing for toxicity by repeated oral administration to Beagle dogs (Range-finding-test); Hoechst Report

Brunk R. (1989) : :Testing for toxicity by repeated oral administration to Beagle dogs (3-month feeding study); Hoechst Report

Brunk R., Mayer, D., Langer, K.-H., Keil, M. (1992) : ; Testing for toxicity by repeated oral administration to Beagle dogs (1-year feeding study); Hoechst Report 92.0935; Doc. A49212

Büttner B., K. Künzler, G. Lemke, B. Haberkorn, H.-M. Kellner (1991) : , Metabolism in male and female rats after a single oral administration of 500 mg/kg body weight; Hoechst Report

Büttner B., K. Künzler, G. Lemke, B. Haberkorn, H.-M. Kellner (1992): , Metabolism in male and female rats after a single oral administration of a nominal dose of 10 mg/kg body weight; Report

Burri R. (1995) : Male rats of a two-generation reproduction study : determination of progesterone and testosterone in plasma after dietary administration; RCC Project No.

Diehl K.-H. & Leist K.-H. (1987a) : : Testing for acute oral toxicity in the male and female Wistar rat; Hoechst Report

Diehl K.-H.& Leist K.-H. (1987b) : :Testing for acute dermal toxicity in the male and female Wistar rat; Hoechst Report

Diehl K.-H. & Leist K.-H. (1987c) : Testing for acute oral toxicity in the male and female NMRI mouse; Hoechst Report

Diehl K.-H. & Leist K.-H. (1987d) : Testing for primary eye irritation in the rabbit; Hoechst Report

Diehl K.-H. & Leist K.-H. (1987e) : Testing for primary dermal irritation in the rabbit; Hoechst Report

Diehl K.-H. & Leist K.-H. (1988a) : Testing for acute intraperitoneal toxicity in the male and female Wistar rat; Hoechst Report

Diehl K.-H. & Leist K.-H. (1988b) : Testing for acute dermal toxicity in the male and female Himalayan rabbit; Hoechst Report

Diehl K.-H. & Leist K.-H. (1988c) : Testing for sensitising properties in the Pirbright White guinea pig according to the technique of BUEHLER; Hoechst Report

Diehl K.-H. & Leist K.-H. (1988e) : Subchronic oral toxicity - dose range finding (28-day feeding study) in the Wistar rat; Hoechst Report

Diehl K.-H. & Leist K.-H. (1988f) : Subchronic oral toxicity - dose range finding - (28-day feeding study) in the NMRI mouse; Hoechst Report

Dotti A., Kinder J., Biedermann, K. (1993a) : Preliminary study to the two-generation reproduction study in the rat; RCC Project

Dotti A., Kinder J., Biedermann, K. (1993b) : Two-generation reproduction study in the rat; RCC Project

Dotti A. & Müller-Kallert H.M. (1993) : Two-generation reproduction study in the rat : report of residue determination of the acive ingredient in fatty tissue samples; RCC Project

van Dijk A. (1992) : Distribution, degradation, metabolism and excretion after repeated oral administration to a lactating goat; RCC Project

Ebert E. (1991) : Testing for acute delayed neurotoxicity in White Leghorn hens; Hoechst Report

Ebert E. (1994) : Repeated - dose dermal toxicity(21 treatments in 30 days) in the Wistar rat; Hoechst Report

Eckert H. G. & Kellner H.-M. (1989): Kinetics in the rat after single oral administration of 500 mg/kg body weight; Hoechst Report

Eckert H. G. & Kellner H.-M. (1990): , Kinetics in the rat after single oral administration of 100 mg/kg body weight; Hoechst Report

Forster R. (1988) : Mitotic gene conversion in Saccharomyces cer. D4; LSR-RTC Report

Grewer T. (1988) : Determination of vapour pressure as a function of temperature of ; Hoechst Report

Heidemann, A. (1988) : Chromosome aberration assay in human lymphocytes in vitro; CCR Project

Hofmann T., Jung R. (1988) : Testing for acute aerosol inhalation toxicity in the male and female Wistar rat . 4-hour LC50; Hoechst Report

Idstein H. (1994) : - Accumulation behaviour of in rat fatty tissue after subchronic feeding of 5 mg/kg active ingredient in the diet; Hoechst Report

Kellner H.-M and G.-D. von Puttkamer (1993a) : Kinetics in the rat: excretion and tissue distribution at different times after a single oral dose of 10 mg/kg or 500 mg/kg to male and female rats; Hoechst Report

Kellner H.-M., J. Maas, G.-D. von Puttkamer (1993b): Kinetics in the rat: excretion and tissue distribution at different times after ten daily oral doses of 10 mg/kg or 500 mg/kg to male and female rats; Hoechst Report

Kramer W., Müller W. (1988) : Evaluation of in the Unscheduled DNA Synthesis test in mammalian cells in vitro; Hoechst Report

Müller W. (1987) : Study of the mutagenic potential in strains of Salmonella typhimurium (Ames test) and Escherichia coli; Hoechst Report

Müller W. (1988a) : Detection of gene mutations in somatic cells in culture HGPRT-test with V79 cells; Hoechst Report

Müller W. (1988b) : Micronucleus test in the male and female NMRI mice after oral administration; Hoechst Report

Ohtsuka M. (1990) : DNA repair test of s Bacillus subtilis; Hita Research Laboratories Repor

Schollmeier U. & Leist K.-H. (1988a) : Testing for sensitizing properties in the Pirbright White guinea pig in a maximization test; Hoechst Report

Schollmeier U. & Leist K.-H. (1988b) : Cumulative dermal toxicity (5 treatments on 5 successive days) in male and female Wistar rat; Hoechst Report

Schollmeier U. & Leist K.-H. (1989a) : Testing for photosensitising properties in the Pirbright White guinea pig; Hoechst Report

Schollmeier U. & Leist K.-H. (1989b) : Subchronic oral toxicity (13-week feeding study) in the Wistar rat; Hoechst Report

Schollmeier U. & Leist K.-H. (1989c) Subchronic oral toxicity (13-week feeding study) in the NMRI mouse; Hoechst Report

Simonnard A. (1992) : Combined chronic toxicity / oncogenicity study by oral route (admixture with the diet) in rats; CIT Report

Simonnard A. (1993) : Combined chronic toxicity oncogenicity study by oral route (admixture with the diet) in mice; CIT Report

Simonnard A. & Provot G. (1995a) : Combined chronic toxicity / oncogenicity study by oral route (admixture with the diet) in rats; 1st amendment - absorption study : determination of residues in brain, liver, kidneys, adipose and testicular tissue; CIT Report

Simonnard A. & Provot G. (1995b) : Combined chronic toxicity oncogenicity study by oral route (admixture with the diet) in mice - 2nd amendment - absorption study determination of residues in adipose and testicular tissue; CIT Report

Stammberger I. (1994) : Testing for toxicity by repeated oral administration to Beagle dogs (1-year feeding study); Hoechst Report

Stumpf K. (1995) : - Summary and evaluation of toxicokinetics, metabolism and bioaccumulation in the animal organism; Report

Till C. P. (1993) : Dermal absorption in rat following a single topical application of test substance at dose levels of 0.001, 0.01 and 0.1 mg/cm^2 skin; Hoechst UK Report

Völkner, W. & Müller E. (1988) : Chromosome aberration assay in bone marrow cells of the Chinese hamster CCR Project

Weinbauer G. (1994) : Assessment of testicular morphology and potential mechanism of pathogenesis in the rat; Hoechst Report

Zietz E. & Spranz E. (1992) : Ruminant feeding study (pretest); Battelle Europe Report

AgrEvo

A company of Hoechst and Schering

Dr. John Klostermyer - Product Safety
Jochen Petersen - Regulatory Affairs Germany
22.10.1996

Dossier on

(technical substance only)

COMPANY SANITIZED

ACTIVE SUBSTANCE:

CONTENT

ACTIVE SUBSTANCE:

CONTENT

4 INFORMATION ON ANALYSIS

4.1 Analytical methods

a lipophilic compound which can easily be determined via the approach of classical GC multimethods developed for organochlorine and organophosphorus compounds, e.g. the DFG S19 method (DFG, 1992, Doc. No.: A50868). The structure does not contain functional groups that allow detection with selective detectors such as ECD or PND, and for this reason GC-MS has to be used. A preferable technique for sensitive quantification and confirmation of the substance would be the selected ion mode (quantification mass: 286; confirmation masses: 151,179, 258).

4.1.1 Air

After adsorption on TENAX-adsorption tubes the active substance is desorbed by hexane elution and subsequent quantification via GC-MS using internal calibration. The limit of detection is 0.2 pg, i.e 0.005 ng/m³ for a typical sampling volume of about 38 L (30 mL/min for 21h).
A detailed description of the method is included in the EMPA report on indoor air contamination by (Wampfler, 1994, Doc. No.: A53081).

4.1.2 Soil

For soil (and plant) material a modification of the DFG S19 method as described under 4.1 using GC-MS technique was used (Idstein et.al., 1990, Doc. No.: A43380). The limit of quantification is 0.01 mg/kg soil.

4.1.3 Water

Water samples can be analysed according to EPA method 608 (EPA, 1982, Doc. No.: A41244). Furthermore GC-MS technique should be used for detection instead of GC-ECD (cf. 4.1).

4.1.4 Blood and urine

No method available.

4.1.5 Organs

Residues of the active ingredient in fat should be determined with the internal method AL11/89-2 (Idstein et. al., 1991, Doc. No.: A45467). Another method was developed for the analysis of in organs (liver, kidney, brain tissue; Idstein et.al., 1990, Doc. No.: A45535). A lower limit of the practical working range of 0.1 mg/kg (brain tissue) and about 1 mg/kg for other organs could be established.

ACTIVE SUBSTANCE:

POINT 4: INFORMATION ON ANALYSIS

4.1.6 **Treated wood**

Determination of the active ingredient in wood powder was performed by a column elution method with a lower limit of the working range of 4 mg/kg (Idstein et.al., 1990, Doc. No.: A45422).

5 INFORMATION ON TOXICOLOGY

(for an extensive review and assessment of toxicology see report

5.1 Toxicity of the active ingredient

5.1.1 Acute toxicity

5.1.1.1 Acute oral

Species	Sex	LD_{50} mg/kg body weight	Reference
NMRI mouse	male/female	> 5,000	A 39392
Wistar rat	male/female	> 5,000	A 39390

Acute oral toxicity testing was carried out in rats and mice at a single oral level of 5,000 mg/kg body weight. Administration of this dose caused slight non-specific signs of intoxication in both rats and mice, but only on the day of treatment; however no deaths occurred. The median lethal dose (LD_{50}) in rats and mice is thus greater than 5,000 mg/kg body weight and is not subject to labelling requirements as defined in European Community Directive 83/467.

5.1.1.2 Acute percutaneous

Species	Sex	LD_{50} (mg/kg body weight)	Reference
Wistar rat	male/female	> 5,000	A 39388
Himalayan rabbit	male/female	> 4,000	A 38556

Acute dermal toxicity testing was carried out in rats at a single dose level of 5,000 mg/kg body weight. Administration of the dose caused no deaths or clinical signs of intoxication. The LD_{50} is thus greater 5,000 mg/kg body weight and is not subject to labelling requirements as defined in European Community Directive 83/467.

In a dermal toxicity study in rabbits, administration of a dose level of 4,000 mg/kg body weight caused no deaths or clinical signs of intoxication. The LD_{50} in the rabbit is thus greater than 4,000 mg/kg body weight.

5.1.1.3 **Acute inhalation**

Five male and five female Wistar SPF rats were exposed to specified concentrations of technical for a duration of 4 hours. Since no animals died as a result of exposure the **4-hour LC_{50} value is >6.61 mg/l air**. This value represents the highest technically administerable dose (300 ml/hour). During and after exposure, the animals showed slight respiratory disturbances and narrowed palpebral fissures. These clinical signs disappeared on the day following inhalation.

A37713

5.1.1.4 **Other routes**

Acute interperitoneal toxicity testing was carried out in rats at a single dose level of 2,000 mg/kg body weight. There were no deaths or clinical signs of intoxication.

A38577

5.1.1.5 **Skin irritation**

Testing for primary skin irritation in the rabbit showed to be **non-irritating** and thus is not subject to labelling requirements as defined in European Community Directive 83/467.

A39389

5.1.1.6 **Eye irritation**

Testing for primary irritation in the rabbit eye was conducted in accordance with EPA Guidelines. Based on this study the test substance is to be classified as **slightly irritating** to the mucosa of the eye and is not subject to labelling requirements as defined in European Community Directive 83/467. A39391

5.1.1.7 **Skin sensitisation**

In a sensitisation test conducted by the technique of Buehler in Pirbright-White guinea pig, the test substance proved to be **non-sensitising** is not subject to labelling requirements as defined in European Community Directive 83/467.

A38803

The test substance also yielded negative results in a maximisation test by the technique of Magnusson & Kligman as well as in a photosensitisation test performed in Pirbright-White guinea pig and is not subject to labelling requirements as defined in European Community Directive 83/467.

A40024, A40579

5.1.2 **Oral 28-day**

4-week feeding study in the rat

(purity 96.8 %) was administered orally to 5 groups, each composed of 5 male and 5 female Wistar rats over a period of 28 days in the daily diet at concentration levels of 0 - 80 - 400 - 2000 or 10000 mg/kg (ppm) diet. Satellite groups consisting of 5 males and 5 females were treated analogously at 0 - 2000 or 10000 ppm, but sacrificed two weeks after termination of the treatment. These concentrations were equivalent to a mean daily substance intake (mg/ kg body weight) of 8.5, 44, 209 and 1019 (males) and 8.0, 41, 195 and 947 (females).

caused a marginal inhibition of body weight gains among the males in the highest treatment group. In addition, the liver weight was moderately increased in the females from the highest dosing group; an effect which proved to be reversible by the end of a 2-week recovery period. No other changes attributable tc in particular changes indicative of an impairment of haematology (red blood cell parameters) or male reproductive organs were noted in any treated group.

Based on these results, the NOEL is considered to be 2000 ppm, equivalent to a mean daily substance intake of 198 mg/kg body weight.

The changes / data in the liver weight and haematology (red blood cell parameters) are summarised in the following table : A40517, A42354

			Dose (mg/kg diet)				
Parameter	**Duration**	**Sex**	**0**	**80**	**400**	**2000**	**10000**
Liver weight (%)	4 wk	M	3.6	3.8	3.7	3.6	3.8
		F	3.8	3.9	4.1	4.1	4.8*
	recovery	M	3.6	-	-	3.8	3.7
	2-wk	F	3.6	-	-	3.9*	3.8
Haematology	4-wk						
RBC		M	7.7	7.4	7.8	7.7	8.1
		F	7.3	7.5	7.6	7.4	7.4
Hb		M	145	145	152	147	160*
		F	139	143	145	142	140
Ht		M	0.45	0.45	0.46	0.44	0.49
		F	0.43	0.44	0.45	0.43	0.43

RBC = erythrocytes (10^{-12}/l; Hb = haemoglobin (g/l); Ht = haematocrit
* = significantly different from the control ($p \leq 0.05$)

4-week feeding study in the dog

(purity 96.8%) was fed in the daily diet to groups of 3 male and 3 female Beagle dogs at concentration levels of 0 - 320 - 1600 or 8000 mg/kg diet (ppm).

Food consumption appeared to be impaired in one male and one female from the highest dose group (8000 ppm); however, no changes in body weight could be observed. Based on the laboratory examinations, the liver and the red blood cells proved to be the target organs: caused an increase in alkaline phosphatase activity at the two highest treatment levels; and also an increase in ALAT (GPT) in two males from the 8000 ppm group. In addition, the absolute (15-23%) and relative (24-29%) liver weight were increased as compared with the controls at 8000 ppm. Although no pathological findings were established by histology, these findings were considered to be an indicator to liver damage. With regard to the red blood cell parameters, a slight decrease in erythrocytes was observed at the 1600 and 8000 ppm dosing levels. In addition, haemoglobin content and haematocrit were reduced in the 8000 ppm dose group.

Based on these results the NOEL can be established at a dietary level of 320 ppm, equivalent to a daily substance intake of approximately 19.3 (19.9 males/ 18.7 females) mg/kg body weight.

The changes in the liver (weight, alkaline phosphatase) and haematology (red blood cell parameters) are summarised in the following table:

A39617, A43329, A46430, A46431

				Dose (mg/kg diet)			
Parameter	**Duration**	**Sex**	**No.**	**0**	**320**	**1600**	**8000**
Liver weight (%)	4-wk	M&F	6	3.22	3.19	3.72	4.06*
Alkaline phosphatase (U/l)	4-wk	M	3	112	113	262	462
		F	3	119	130	304	613
		M&F	6	116	122	283	538
Haematology	4-wk						
RBC		M&F	6	7.56	7.11	6.83*	6.73*
Hb		M&F	6	172	156	158	154*
Ht		M&F	6	0.54	0.51	0.49	0.47*

RBC = erythrocytes (10^{-12}/l; Hb = haemoglobin (g/l); Ht = haematocrit;
* = significantly different from the control ($p \leq 0.05$);
Note : According to the report statistical analysis was carried out in the case of liver weights and haematology on the basis of pooled males and female values; no statistical analysis was performed in the case of alkaline phosphatase.

4-week feeding study in the mouse

(purity 96.8 %) was administered orally to 5 groups, each composed of 5 male and 5 female NMRI mice, in the daily diet at concentration levels of 0 - 80 - 400 - 2000 or 10000 mg/kg (ppm) diet over a period of 28 days. Satellite groups, consisting of 5 males and 5 females, were treated in the same way at 0 - 2000 or 10000 ppm, but sacrificed two weeks after termination of treatment. These concentrations were equivalent to a mean daily substance intake (mg/kg body weight) of 15.9, 87, 471 and 1937 (males) and 18.5, 102, 514 and 2552 (females).

The liver weight was slightly increased at 10000 ppm. This effect proved to be reversible by the end of the 2-week recovery period. The slightly higher liver weights at 2000 and 10000 ppm in the females after the 2-week recovery period are considered to be related to the low control value. Clinical chemistry parameters indicative of an impairment of the hepatic functions such as GOT, GPT or alkaline phosphatase were not measured in this study due to the limited amount of serum available. The haematology parameters indicated no changes in the sense of anaemia.

Based on a slight increase in liver weights at 10000 ppm, the No Observable Effect Level (NOEL) is considered to be 2000 ppm; this dietary level was equivalent to a mean daily substance intake of 472 and 514 mg/kg body weight in the males and females, respectively.

The changes in the liver weights and red blood cell parameters are summarised in the following table: A39616, A46427

			Dose (mg/kg diet)				
Parameter	**Duration**	**Sex**	**0**	**80**	**400**	**2000**	**10000**
Liver weight (%)	4-wk	M	4.7	4.9	4.9	5.2	5.7*
		F	4.4	4.5	4.4	4.9	5.1*
	recovery	M	4.9	-	-	5.0	4.7
	2-wk	F	4.2	-	-	4.9*	4.7*
Haematology	4-wk						
RBC		M	9.4	9.2	9.5	9.2	9.5
		F	9.3	9.4	9.7	9.2	9.2
Hb		M	174	169	178	171	174
		F	174	176	182	173	170
Ht		M	0.50	0.49	0.51	049	0.49
		F	0.50	0.49	0.52	0.48	0.48
Reticulocytes		M	0.084	-	-	-	0.072
		F	0.082	-	-	-	0.077

RBC = erythrocytes (10^{-12}/l; Hb = haemoglobin (g/l); Ht = haematocrit
* = significantly different from the control ($p \leq 0.05$)

5.1.2.1 Percutaneous route - cumulative toxicity (28-day study) - rat

Preliminary study

In a cumulative dermal toxicity study in rats (96.8%) was applied without a carrier on five consecutive days - each for 6 hours/day - to the shaved nape skin under an occlusive bandage. Two groups, each composed of 6 male and 6 female rats, were treated at dose levels of 0 or 1000 mg/kg body weight. After the final dermal treatment the animals were kept under observation for another 3 days. Clinical observations, food consumption, body weight and necropsy indicated no changes attributable to the treatment.

A40925, A44611, A46428

Main study

In a repeated-dose dermal toxicity study in rats - 21 applications, each for 6 hours/day, 5 days per week over a period of 30 days - was applied to the shaved nape skin under an occlusive bandage. Four groups, each composed of 5 male and 5 female rats, were treated at dose levels of 0 - 100 - 300 or 1000 mg/kg body weight, using PEG 400 as vehicle. Satellite groups of 5 males

and 5 females were treated analogously with 0 - 300 or 1000 ppm, but sacrificed four weeks after the termination of treatment.

No findings of toxicological significance could be detected in any testing group at the end of the 4-week treatment period. In addition, in the form of an emulsion in PEG 400 proved to be non-irritating to the treated skin area. At the end of the 4-week recovery period the testicular weights showed a tendency to decrease by about 10-15% as compared with the control, resulting in a statistically significant change in the relative organ weight. Taking into account the slight degree of the changes and the absence of any dose-dependency, the significance of the finding was considered to be doubtful.

Thus, the No Observable Adverse Effect Level (NOAEL) for systemic toxicity was considered to be 1000 mg/kg body weight per day.

A52888

5.1.3 Sub chronic toxicity (90-day)

5.1.3.1 90-day feeding study

feeding study in rats

(purity 96.8%) was administered to 5 groups, each composed of 10 male and 10 female Wistar rats, in the daily diet at concentration levels of 0 - 80 - 400 - 2000 or 10000 mg/kg (ppm) diet over a period of 13 weeks. Satellite groups, consisting of 10 males and 10 females, were treated in the same way at 0 - 2000 or 10000 ppm, but sacrificed four weeks after termination of the treatment. These concentrations were equivalent to a mean daily substance intake (mg/kg body weight) of 6.7, 33, 166 and 827 (males) and 7.0, 35, 170, and 819 (females).

caused slight to moderate increases in liver weights at 10000 ppm in both sexes; this effect was largely reversible after 4 weeks of recovery. No histopathological changes were observed. In addition, slight decreases in erythrocytes, haemoglobin content and haematocrit values were observed in the males from the highest dosing group at the end of the treatment period; this change, which could not be detected at the end of the 4-wk recovery period, may possibly have been treatment-related. No other changes attributable to the test substance were found in any of the treated groups.

Based on the liver and marginal haematology findings, the NOEL is considered to be 2000 ppm (diet), equivalent to a mean daily substance intake of 168 mg/kg body weight.

Note: A slight decrease in testicular weight at 2000 and 10000 ppm was seen at the end of treatment and more marked at the end of the 4-wk recovery period at 10000 ppm. In addition, four males - two males each of the main and recovery groups - showed tubular atrophy (grade 1 and 3); only one control (recovery) was noted with this finding (grade 1).

The changes in liver weight and haematology (red blood cell parameters) are summarised in the following table:

A40925, A44611, A46428

			Dose (mg/kg diet)				
Parameter	**Duration**	**Sex**	**0**	**80**	**400**	**2000**	**10000**
Liver weight (%)	13 wk	M	3.2	3.3	3.4	3.5	3.8*
		F	3.2	3.5	3.3	3.5	3.7*
	recovery	M	3.0	-	-	3.1	3.2*
	4-wk	F	3.2	-	-	3.1	3.3
Haematology	13-wk						
RBC		M	8.4	8.3	8.4	8.3	8.0*
		F	7.9	7.8	7.6	8.1	7.7
Hb		M	150	150	152	149	146
		F	142	141	137	148	142
Ht		M	0.45	0.44	0.46	0.44	0.42*
		F	0.43	042	0.42	0.45	0.42

RBC = erythrocytes (10^{-12}/l; Hb = haemoglobin (g/l); Ht = haematocrit
* = significantly different from the control ($p \leq 0.05$)

5.1.3.2 Rat dermal

Not available see 28 day study

5.1.3.3 Rat inhalation

A short-term inhalation study in rats was not conducted, because human exposure to via the inhalation route is unlikely for the following reasons:

- The vapour pressure of is very low, i.e. 5.5×10^{-6} at 25 °C (Grewer 1988) and thus no relevant inhalation exposure of vapour is possible.

- is an oily liquid; therefore the formation of inhalable fine dust is not possible.

5.1.3.4 **Other animal species oral**

3-month feeding study in dogs

Groups of beagles (4 animals/sex/group) received (95.8 %) at dietary levels of 0 - 320 - 1600 or 8000 ppm for 3 months. Satellite groups consisting of 2 males and 2 females were treated analogously at 0 - 1600 or 8000 ppm, but sacrificed four weeks after the termination of treatment.

Feeding at 320, 1600 and 8000 ppm over a period of 3 months caused a moderate to marked increase in liver weights in both sexes; in addition, the activity of the alkaline phosphatase (ALP) and ALAT (GPT) were increased at the 8000 ppm level. A clear tendency of increased alkaline phosphatase was already recognisable in the 1600 ppm dosing group. Determination of ALP after 6-wk treatment revealed a dose-dependent increase from 320 ppm onwards in the males and from 1600 ppm onwards in the females; GOT and GPT values were also increased at the highest dose level. All other changes proved to be completely reversible after 4 weeks of recovery, except for the ALP value in the highest dose group. Although no corresponding pathological changes were observed, these findings are considered to be indicative of liver damage. With regard to the red blood cell parameters, slight decreases in erythrocytes, haemoglobin content and haematocrit were observed in both sexes at the 1600 and 8000 ppm dosing levels at the end of treatment. This effect was not detectable after the 4-wk recovery period. Measurement after a 6-wk treatment period revealed only faint signs of this effect at the 8000 ppm level. In addition, there was a higher frequency in diarrhoea in both these groups and some of the dogs in the highest dose group showed a temporary impairment of food consumption.

Based on the increases in liver weights in connection with the increase in ALP, a NOEL of slightly less than 320 ppm can be derived; this is equivalent to a mean daily substance intake of less than 22.8 (24.1 males/ 21.5 females) mg/kg body weight for both sexes.

The changes in the liver (weight, alkaline phosphatase) and haematology (red blood cell parameters) are summarised in the following table:

				Dose (mg/kg diet)			
Parameter	**Duration**	**Sex**	**No.**	**0**	**320**	**1600**	**8000**
Liver weight (%)	13 wk	M&F	8	2.95	3.70*	3.76*	4.54*
	4-wk recovery	M &F	4	3.45	-	3.33	3.41
Alkaline phosphatase (U/l)	6 wk	M	6	192	273*	327*	739*
		F	6	192	199	351*	689*
	13 wk	M	6[a]	179	212	296	872*
		F	6[a]	154	155	310	689*
	4-wk recovery	M	2	106	-	124	324
		F	2	117	-	123	226
ALAT(GPT) (U/l)	6 wk	M	6	17	16	17	45*
		F	6	18	16	15	51
	13 wk	M	6[a]	22	21	37	43*
		F	6[a]	21	19	22	39*
	4-wk recovery	M	2	24	-	22	28
		F	2	16	-	21	26
Haematology	6-wk						
RBC		M&F	12	6.68	6.59	6.36	6.12
HB		M&F	12	151	150	146	139*
HK		M&F	12	0.47	0.47	0.46	0.44*
Haematology	13-wk						
RBC		M&F	12	6.93	6.65	6.26*	6.21*
HB		M&F	12	154	149	143*	142*
HK		M&F	12	0.49	0.46	0.45	0.44*
RBC	4-wk recovery	M&F	4	6.60	-	6.45	6.64
HB		M&F	4	151	-	147	152
HK		M&F	4	0.49	-	0.46	0.48

RBC = erythrocytes (10^{-12}/l; Hb = haemoglobin (g/l); Ht = haematocrit

* = significantly different from the control ($p \leq 0.05$)

[a] = no. of animals at 320 ppm = 4;

13-week feeding study in mice

(purity 96.8 %) was administered orally to 5 groups, each composed of 10 male and 10 female NMRI mice, in the daily diet at concentration levels of 0 - 80 - 400 - 2000 or 10000 mg/kg (ppm) diet over a period of 13 weeks. These concentrations were equivalent to a mean daily substance intake (mg/kg body weight) of 14, 70, 338 and 1668 (males) and 15, 70, 353 and 2003 (females).

caused a moderate increase in liver weights at 10000 ppm in both sexes; however, no histological correlate was found. Remark: Clinico-chemical parameters indicative of an impairment of the hepatic functions such as GOT, GPT or alkaline phosphatase were not measured in this study due to the limited amount of serum available.

Haematology revealed a slight decrease in erythrocytes, haemoglobin and haematocrit value and a marginal increase in reticulocytes in the males from the highest dosing group. No other substance-related changes were established.

Based on these findings, the NOEL was established at a concentration of 2000 ppm, equivalent to an average daily substance intake of 338 and 353 mg/kg body weight in the males and females, respectively.

The changes in the liver weight and red blood cell parameters are summarised in the following table: A40796, A46426

			Dose (mg/kg diet)				
Parameter	**Duration**	**Sex**	**0**	**80**	**400**	**2000**	**10000**
Liver weight (%)	13 wk	M	4.0	3.8	4.0	3.9	4.7*
		F	3.8	3.7	4.0	4.0	5.8*
Haematology	13 wk						
RBC		M	9.4	9.0	9.1	9.2	8.7*
		F	9.3	9.3	9.1	9.1	9.1
Hb		M	175	171	172	169	163*
		F	175	174	172	172	172
Ht		M	049	0.47	0.47	047	0.44*
		F	0.49	0.49	0.48	0.48	0.48
Reticulocytes		M	0.037	-	-	-	0.043*
		F	0.037	-	-	-	0.038

RBC = erythrocytes (10^{-12}/l; Hb = haemoglobin (g/l); Ht = haematocrit
* = significantly different from the control ($p \leq 0.05$)

5.1.4 Chronic toxicity

5.1.4.1 Oral

Chronic oral (feeding) toxicity and carcinogenicity in rats

ACTIVE SUBSTANCE:

POINT 5: INFORMATION ON TOXICOLOGY

In a combined chronic toxicity and carcinogenicity study, (lots of 94.0 and 95.4% purity) was fed to Sprague-Dawley rats (110 males and 110 females/group) in the diet at concentrations of 0, 400, 2000, 10000 or 20000 ppm for two years. These concentrations were equivalent to a mean daily substance intake (mg/kg body weight) of 20, 101, 500 and 1022 (males) and 26, 130, 661 and 1335 (females). Twenty rats per sex and group were killed after 12 months and 24 months respectively in order to evaluate chronic toxicity. Fifty rats per sex and group were scheduled for sacrifice after 104 weeks to evaluate the carcinogenic potential. Further 20 rats per sex and group were scheduled for residue determinations in various tissues at different times in view of the lipophilic nature of this part of study is reported under section 1.4.

Treatment at 10000 and 20000 ppm caused a slight to moderate increase in the frequency of clinical signs (round back, emaciation, chromorhinorrhoea, soft faeces) in the males, decrease in food consumption and body weight gain and decrease in triglycerides (including at 2000 ppm) and increase in cholesterol (females only).

Organ weight analysis and pathology identified the liver and male reproductive organs (testes and epididymides) as target organs. No changes attributable to the test substance were observed in the red blood cell parameters at any of the examination times.

An increase in liver weight together with centrilobular hepatic cell hypertrophy was found in both sexes at 2000 ppm and higher dose levels.

The effects on the male reproductive organs consisted in an increase in soft consistency and reduction in size of testes and epididymides associated histologically with degeneration of seminiferous tubules and inhibition of spermatogenesis in the testes and oligospermia and small tubules in the epididymides from 2000 ppm onwards; there was also an decrease in testicular weight at 10000 and 20000 ppm.

An increase in foamy alveolar macrophages in the lungs was also noted at 2000 ppm and higher doses after 104 weeks, but only in the females.

Based on these results the NOAEL was considered to 400 ppm, which is equivalent to a mean daily substance intake of 20 mg/kg body weight. No indication of any carcinogenic potential was found up to and including the 20000 ppm level.

The changes in the liver, testes and lungs are summarised in the following table:

ACTIVE SUBSTANCE:

POINT 5: INFORMATION ON TOXICOLOGY

104-wk rat study - toxic effects

Parameter	Duration	Sex	No.	Dose (mg/kg diet) 0	400	2000	10000	20000
LIVER	52 wk	M	10	2.9	3.0	3.2	3.5*	3.6*
Weight (%)		F	10	2.8	3.1	3.5*	4.1*	4.1*
	104 wk	M	10	2.4	3.0	2.5	2.7	3.2*
		F	10	2.9	3.2	3.3	4.2*	4.1*
Pathology	52 wk	M	20	/	/	/	13	12
Hypertrophy		F	20	/	/	/	11	17
	104 wk	M	70	/	/	18	31	27
		F	70	/	/	38	59	50
TESTES	52 wk	M	10	0.55	0.61	0.59	0.36*	0.30*
Weight (%)	104 wk	M	10	0.52	0.60	0.55	0.21	0.19*
Pathology - Bilateral changes								
Testes	52 wk	M	20	/	/	2	17	17
Soft	104 wk	M	70	7	7	27	58	59
Reduction in	52 wk	M	20	/	/	2	16	19
size	104 wk	M	70	1	6	19	56	61
DegTub	52 wk	M	20	/	/	2	18	18
	104 wk	M	70	2	2	16	62	67
InhibSperm	52 wk	M	20	/	/	3	17	18
	104 wk	M	70	2	3	16	62	67
InterOed	52 wk	M	20	/	/	3	16	15
	104 wk	M	70	/	/	/	/	/
EPIDIDYMIDES - Bilateral changes								
Reduction in	52 wk	M	20	/	/	2	4	6
size	104 wk	M	70	2	7	18	30	43
OligoSperm	52 wk	M	20	/	/	3	20	18
	104 wk	M	70	2	3	15	62	67
RedTub	52 wk	M	20	/	/	2	2	/
	104 wk	M	70	/	/	6	12	13
EpithAtroph	52 wk	M	20	/	/	/	/	/
	104 wk	M	70	/	/	4	30	26
LUNGS - Foamy alveolar macrophages								
	104 wk	F	70	10	4	17	37	45

DegTub = degeneration of seminiferous tubules; InhibSperm = inhibition of spermatogenesis
InterOed = interstitial oedema; OligoSperm = oligospermia;
RedTub = tubules reduced in size; EpithAtroph = epithelial cell atrophy;
* = significantly different from control ($p \leq 0.05$);

1-year feeding study in the dog

Groups of beagles (6 animals/sex/group) received (95.8%) at dietary levels of 0 - 320 - 1600 or 8000 ppm for 1 year. Satellite groups consisting of 2 males and 2 females were treated analogously at the same dietary levels, but sacrificed after 6 months of treatment. These concentrations were equivalent to a mean daily substance intake (mg/ kg body weight) of 0, 24, 129 and 592 (males) and 0, 21, 115 and 575 (females). In addition, various tissues were taken for residue determinations in view of the lipophilic nature of ; this part of the study is reported under section 1.4.

Food consumption appeared to be impaired in the highest dose group (8000 ppm); however, no changes in body weight could be observed. Some dogs from the two highest dose groups showed more or less marked non-dose-related deterioration of general health; one male dog from the highest dose group died on day 323 of treatment; an advanced stage of liver fibrosis with nodular change and expansive necroses was histologically evident.

Haematology - Slightly reduced erythrocyte counts were matched by correspondingly slight reductions of haemoglobin concentrations; these findings which were transitory and no longer present at the end of the study were found more frequently at 8000 ppm and occasionally at 1600 ppm.

Clinical chemistry parameters - Feeding at 1600 and 8000 ppm caused a consistent dose-related and marked increase in alkaline phosphatase in both sexes. In addition, an increase in ALAT (GPT) and ASAT (GOT) occurred more frequently at 8000 ppm. The changes in ALAT and ASAT observed at all dose levels after 1-month treatment were very slight in degree and showed no dose-dependency; therefore, a treatment-relationship appears to be unlikely. A slight to medium decrease in cholesterol was also found in the two highest dose groups, but not consistently at all examination times.

Organ weights - At the 6-month sacrifice, the relative liver weights were increased in all treated groups. The dogs killed after 12 months showed increases, except for the 1600 and 8000 ppm groups; in the 8000 ppm group, the absolute weights were also increased. In all cases, the increase in liver weights showed a clear dose-dependency and is therefore considered to be substance-related. In addition, the relative adrenal weight was increased in the middle and highest dose groups.

Pathology - After 6 months of treatment, hypereosinophilic hepatocytes were found in periportal areas in the liver of some animals from all treatment groups. At 8000 ppm, one male dog died of liver failure (jaundice) on day 323. Histologically, an advanced stage of liver fibrosis with nodular change and

expansive necroses was evident. Another female dog from this group which survived until the end of the study had developed a more moderate stage of hepatic fibrosis. In the liver of other animals treated at 1600 ppm (one female) and 8000 ppm (four males and one female), interlobular interseptal connective tissue formation could be found. Hypereosinophilic hepatocytes in periportal areas as well as atrophy of the adrenal zona fascicularis occurred sporadically in all treated groups. However, hypereosinophilic hepatocytes as well as atrophy of the adrenal zona fascicularis were not associated with any cell or tissue lesions. For this reason and because of their reversibility, these changes were interpreted as toxicologically not relevant, but considered to be an adaptive phenomenon.

Assessment - Based on these results, the "No Toxic Effect Level" was considered to be approximately 320 ppm, equivalent to a mean daily substance intake of 23.7 and 21.4 mg/kg body weight for the male and female dogs, respectively.

Re-evaluation - However, based on the slight increase in liver weight at 320 ppm at the 6-month interim kill, the "No Toxic Effect Level" can be considered to be slightly lower than 320 ppm.

A49212

1-year dog - toxic effects in liver and haematology

Parameter	Duration	Sex	No.	Dose (mg/kg diet) 0	320	1600	8000
Liver weight (%)	6 months	M&F	4	3.29	3.87*	3.97*	4.64*
	12 months	M&F	12	3.37	3.69	4.34*	4.55*
Alkaline phosphatase (U/l)	6 weeks	M&F	16	146	170	277*	358*
	3 months	M&F	16	135	161	261*	396*
	6 months	M&F	16	94	129	220(m)	346*
	9 months	M&F	12	89	120	225	413(m)
	12 months	M&F	12	86	115	217*	418*

to be killed prematurely; all of them due to poor health condition. These findings could not be attributed to treatment with the test substance.

With a view to the liver as possible target organ the results indicate a consistent distinct increase in ALP in both sexes at all examination times and a slight increase in liver weight in the high dose females. No changes were observed in GOT and GPT activities and histopathology revealed no substance-related changes either.

Haematology revealed a slight, but consistent decrease in erythrocytes and haemoglobin content in the females over the whole study period; a tendency towards this effect was also recognisable in the males at the highest dose (1600 ppm).

All other examinations, including the special measurement of serum testosterone and urinary cortisol, indicated no substance-related changes.

Based on these considerations, the NOEL was established to be 160 ppm (diet), equivalent to a mean daily substance intake of 11.4 mg/kg body weight.

A52591

Add-on 1-year dog - toxic effects

Parameter	Duration	Sex	No.	Dose (mg/kg diet) 0	60	160	1600
Liver weight (%)	12 months	M	5-6	3.48	3.72	3.59	3.73
		F	4-6	3.93	4.04	3.97	4.53*
Alkaline phosphatase (U/l)	6 weeks	M&F	12	144	148	151	247*
	3 months	M&F	12	109	116	117	214*
	6 months	M&F	12	87	97	100	161(m)
	9 months	M&F	12	72	92	87	192*
	12 months	M&F	12	63	68	84(f)	176*

Add-on 1-year dog - toxic effects				Dose (mg/kg diet)			
Parameter	Duration	Sex	No.	0	60	160	1600
Haematology							
RBC	6 weeks	M&F	12	6.64	6.36	6.62	6.28
	3 months	M&F	12	6.36	6.23	6.26	5.88(f)
	6 months	M&F	12	6.44	6.45	6.41	5.94(f)
	9 months	M&F	12	6.42	6.15	6.48	5.91(f)
	12 months	M&F	12	6.58	6.38	6.54	5.89(f)
Hb	6 weeks	M&F	12	152	148	155	144
	3 months	M&F	12	148	146	146	136(f)
	6 months	M&F	12	150	152	152	139(f)
	9 months	M&F	12	151	147	154	140(f)
	12 months	M&F	12	154	148	155	139(f)
Ht	6 weeks	M&F	12	0.45	0.44	0.45	0.42
	3 months	M&F	12	0.44	0.43	0.43	0.40(f)
	6 months	M&F	12	0.44	0.44	0.44	0.41(f)
	9 months	M&F	12	0.44	0.43	0.44	0.41(f)*
	12 months	M&F	12	0.45	0.43	0.45	0.40(f)

RBC = erythrocytes (10^{-12}/l; Hb = haemoglobin (g/l);
* = significantly different from the control ($p \leq 0.05$)
(m) = only male value statistically significant;
(f) = only female value statistically significant;
(f)* = reticulocytes in females show statistically significant increase

Combined chronic toxicity and oncogenicity study in mice

In a combined chronic toxicity / oncogenicity study, (96.1% purity) was fed to Swiss mice (90 males and 90 females/group) in the diet at concentrations of 0, 400, 3500, or 7000 ppm for two 97 weeks. These concentrations were equivalent to a mean daily substance intake (mg/kg body weight) of 68, 615 and 1271 (males) and 83, 728 and 1481 (females). Twenty mice per sex and group were killed after 52 weeks, in order to evaluate chronic toxicity. Fifty mice per sex and group were scheduled for sacrifice after 97 weeks to evaluate the carcinogenic potential. Further 20 mice per sex and group were scheduled for residue determinations in various tissues at different times in view of the lipophilic nature of :this part of the study is reported under section 1.4..

ACTIVE SUBSTANCE:

POINT 5: INFORMATION ON TOXICOLOGY

Treatment with was generally well tolerated; from week 80 onwards, a slightly higher mortality was observed in males given 7000 ppm and from week 53 a slightly lower (up to 5 %) body weight in the males of the two highest dose groups. The only changes of toxicological significance were an increase in liver weights (up to 25 %) at week 52 and 97 in line with hepatocellular hypertrophy in both sexes at 3500 and 7000 ppm at week 97.

Haematology indicated no impairment of the red blood cell parameters at the different examination times.

Based on these results the NOAEL was considered to 400 ppm, which was equivalent to a mean daily substance intake of 68 and 83 mg/kg body weight in the males and females, respectively.

In addition, showed neither carcinogenic potential nor any effect on the incidence of spontaneously occurring tumours. Moreover, no decrease in latency of tumour appearance was observed.

The non-neoplastic and neoplastic changes in the liver are shown in the following table.

A49488

2-year mouse - toxic effects

Parameter	Duration	Sex	No.	Dose (mg/ kg diet) 0	400	3500	7000
Liver Weight (%)	52 wk	M	10	4.9	4.8	5.7*	6.1*
		F	10	4.9	5.0	6.2*	6.6*
	97 wk	M	26 - 40	5.8	5.3	7.3*	6.7*
		F	24 - 31	5.3	4.9	5.9*	6.6*
Hepatocell. Hypertrophy	52 wk	M	20	/	/	/	/
		F	20	/	/	/	/
	97 wk	M	50	/	/	8	22
		F	50	/	/	1	23
Hepatocell. Adenoma	52 wk	M	20	/	/	1	/
		F	20	/	/	/	/
	97 wk	M	50	8	8	9	8
		F	50	/	1	/	1
Hepatocell. Carcinoma	52 wk	M	20	/	/	1	/
		F	20	/	/	/	/
	97 wk	M	50	5	1	8	7
		F	50	/	/	1	/

* = stat. significantly different from control ($p \leq 0.05$)

5.1.4.2 **Rat inhalation**

Not available

5.1.5 **Metabolism**

Absorption, distribution and excretion studies following both oral and percutaneous administration

Rat - single oral application

Excretion data were obtained in rats after single oral application of 10 to 500 mg / kg body weight. Normally 60 to 90% of the applied radioactivity was excreted after 24 hours, and recovery after 7 days was greater than 95%. Up to 4% of the administered amount was still present in the organs after 7 days. The predominant portion (> 90%) was excreted via faeces and only 1 to 3.5% via urine, with higher values among the male rats. Excretion in most cases was biphasic, with mean half-lives of 7 and 50 hours, the times for faeces and urine being about the same.

A45183, A48709, A41503, A44064, A50094

Rat - repeated oral administration

The rapid elimination was also evident during the repeated treatment studies (10 x 10 mg/kg and 10 x 500 mg/kg body weight, ten times radiolabelled), in which about 90% of the hitherto administered amount were excreted within 24 hours. Up to 5% of the administered amount was still present in the organs after 7 days. Renal and faecal elimination was similar to that in single dose studies, but it was delayed after repeated administration.

A51063

Gastro-intestinal (oral) absorption

All kinetics and metabolism studies conducted with generally indicate a low rate of oral absorption. Based on a special absorption and biliary excretion study in female rats (Büttner 1992), biliary excretion plays a relevant role in the excretion of absorbed ; however, the result of this study (about 5 % absorption) must be considered to be of very limited value with respect to the quantitative aspects, because the experiment was performed with narcotised rats,

the very limited physiological activity of which resulted in artificially low absorption. A situation of this kind may present major problems and uncertainties when it comes to estimating the biliary excretion rate of absorbed material, particularly in studies where the amounts of the compound incorporated in the organ and tissues are determined a relatively long time after oral administration.

Based on these considerations and with a view to an assessment of human health risk resulting from prolonged low-dose exposure, the study of Kellner et al. 1993b appears to be the most appropriate for an estimation of gastro-intestinal absorption.

On the basis of the radioactivity measurements in urine and tissues/organs after repeated oral application of low (10 mg/kg) doses determined 4 hours after the last dosing, the minimum oral absorption rates (tissue excl. gastro-intestinal tract plus urine) were estimated to be 13.2 and 12.4 % in the female and male rat, respectively. The corresponding values from the high (500 mg/kg) dosing were considerably lower (less than 4 %).

The relevant data of this study are summarised in the following table :

A48709, A51063

Minimum oral absorption rate (%) in the rat following repeated (10 times) oral exposure						
	low dose (10 mg/kg b.w.)			high dose (500 mg/kg b.w.)		
rat	urine	tissues	absorption	urine	tissues	absorption
male	3.91	8.5	**12.4**	1.66	2.08	3.7
female	0.64	12.53	13.2	0.6	3.2	3.8
radioactivity found 4 hours after the last (10th) dosing						

Rat - single percutaneous administration

Absorption of ^{14}C-labelled was studied in 72 male rats following single dermal application of 0.001, 0.01 and 0.11 mg / cm^2 (dose per animal) in the form of , a representative emulsifiable concentrate formulation. Each dose group consisted of 24 animals which were killed in subgroups of 4 animals after exposure times of 0.5, 1.0, 2.0, 4.0, 10 and 24 hours. The percentage dose absorbed, as measured by the direct method, was

rather variable over the 24 hour period as shown in the table below.

nominal dose	dermal absorption (% applied dose) after 24 hours of exposure				
mg / cm^2 skin	urine	faeces	carcass	total	recovery
0.1	0.37	0.15	5.71	6.23	83.0
0.01	0.23	0.08	2.51	2.82	92.0
0.001	0.51	0.28	11.46	**12.25**	93.0

For an assessment of human health risk resulting from prolonged low-dose exposure, the dermal absorption rate of 12.25 % determined at the lowest dose level appears to be the most appropriate value.

A49560

Elucidation of metabolic pathways (for references see section: *absorption, distribution and excretion studies following both oral and percutaneous administration* above)

The main component in faeces is , making up 60 to 80% of the applied amount. Up to 10% of the applied amount are present in the form of the de-ethylated metabolite . The other (unknown) metabolites in faeces are in each case considerably less than 10%.

In urine, and (benzoic acid and benzyl alcohol structure, from the diphenyl ether moiety of the molecule) are found in free and conjugated (sulphate) form. However, in view of the small amounts excreted via urine and their ready solubility in water, they are of no significance for the overall residue pattern.

In general it should be noted that, if the applied amount is taken as the reference magnitude, is a substance which metabolises only to a very low extent. However, if the absorbed portion is taken into account, it will be seen that this is almost completely metabolised.

Most of the metabolites are excreted via the faeces, since only was present in faeces after fistulisation of the bileduct. In the faeces from day 2 onwards (not relevant from the quantitative viewpoint), the metabolite portion increased relative to intact active ingredient (Büttner et al. 1992).

ACTIVE SUBSTANCE:

POINT 5: INFORMATION ON TOXICOLOGY

Biokinetics and metabolism in farm animals

Ruminant feeding study (Pretest)

Two diary cows received daily in doses equivalent to 1 or 10 mg/kg diet (ppm) over a period of 10 weeks. The high-dose cow was killed 1 day after the last dosing, the low-dose cow after a depuration period of 23 days. During the treatment and depuration period two milk samples were taken daily and analysed for residues. After slaughtering, tissue samples of fat, muscle, diaphragm, liver, kidneys and blood were also analysed for residues. The plateau concentration in milk was reached very rapidly, i.e. two days after the commencement of treatment. Except in fat tissue, no - or only negligible tissue residues were found. The residues in the milk (plateau average concentration) and body fat are shown in the following table :

	examination time	residue concentration (ppm)			bioconcentration factor (BCF)		
		body fat	milk fat	milk	body fat	milk fat	milk
Cow 1 (1 ppm)	plateau concentration	-	0.7	0.03	-	0. 7	0.03
	23 day p.a.	0.36	< DL	< DL	0.36		
Cow 2 (10 ppm)	plateau concentration		8.9	0.35		0.89	0.035
	1 day p.a.	5.8	-	-	0.58	-	-

ppm = mg/kg; p.a. = after the end of treatment; < DL = below detection limit of 0.005mg/l

These results indicate a transfer of into the cow milk fat at concentrations slightly higher than those in the body fat. However, due to a fat content of about 5 % in the milk, the concentration of in the milk must be considered to be very low in view of the BCF values of 0.03. In addition, it is worth noting that the residue level in milk (fat) declined rapidly after the termination of treatment and after 3 days declination period no residues could be detected; this observation permits the conclusion that no or very low amounts of may be released from the body fat into the milk under normal intuitive conditions.

A48022

Metabolism in lactating goats

In this study, lactating goats received ^{14}C- labelled on three consecutive days at a dose level of 5.3 mg/kg body weight to elucidate the absorption, distribution, metabolism and excretion. In addition, the concentration profile of radioactivity in milk and the excretion pattern via urine and faeces were monitored. Two hours after the last dosing the animals were killed for elucidation of residues in edible tissues.

The excretion of mainly proceeded via the faeces. Only low amounts were excreted in urine (0.8%) and milk (1.3%). The highest ^{14}C-levels were found in the liver (76 ppm) and at a considerably lower level in milk (2.9 ppm), kidneys (2.4 ppm), fat (1.3 ppm) and muscle (0.7 ppm).

In the other organs and in the milk, only parent compound was detected.

A48907

Residues of in adipose and other tissues of mammalian species

has a high partition coefficient for octanol/water (log P_{OW}) of 8.2. For this reason it had been expected to accumulate in fat, and a series of studies and residue analyses in connection with toxicity studies in rat, mouse and dog were conducted to determine the bioconcentration factor (BCF). The BCF is defined as the quotient of the test substance concentration in fat and administered diet.

Residue concentrations in fat :

Considerably high residue concentrations of were measured in adipose tissue at all examination times. However, the plateau (steady-state) concentrations at the different dosing levels were reached within an exposure period of 3 to 12 months. The residue concentrations measured in the different dosing groups showed a clear dose-dependency. In general, the residue concentrations in dogs and mice were comparable in both sexes, but in the rat frequently somewhat higher in the females. Particularly during the first 52 weeks of exposure, no relevant differences could be observed between subcutaneous and retroperitoneal fat, although the residues in retroperitoneal fat were often slightly higher than in subcutaneous fat. The following table summarises the residues in fat after low dose exposure obtained in the different toxicological or special residue studies.

type of study	diet	plateau concentration			elimination	reference
	(ppm)	time (month)	ppm	BCF	half-life (day)	
accumulation rat, female*	5	12^{sc}-14^{rp}	$13^{sc}/20^{rp}$	$2.7^{sc}/3.9^{rp}$	39^{sc}-47^{rp}	A51952 A52015 A51491
2-year toxicity rat	400	9	1147	**2.9**	ND	A54530
2-year toxicity mouse	400	3	1986	**5**	ND	A54531
1-year toxicity dog	60	6	246	**4.1**	ND	A52591
1-year toxicity dog	320	6	1681	**5.3**	ND	A49212

1-year dog - toxic effects in liver and haematology				Dose (mg/kg diet)			
Parameter	**Duration**	**Sex**	**No.**	**0**	**320**	**1600**	**8000**
Haematology							
RBC	6 weeks	M&F	16	6.20	6.29	5.93*	5.74*
	3 months	M&F	16	6.50	6.25(m)	5.96(m)	5.79(m)
	6 months	M&F	16	6.63	6.25(m)	5.94(m)	5.80(m)
	9 months	M&F	12	6.66	6.54	6.01*	6.04*
	12 months	M&F	12	6.60	6.49	6.15*	6.12*
Hb	6 weeks	M&F	16	145	146	139	134*
	3 months	M&F	16	152	148(m)	143(m)	138(m)
	6 months	M&F	16	156	149(m)	143(m)	139(m)
	9 months	M&F	12	158	155	145*	145*
	12 months	M&F	12	156	159	147	147
Ht	6 weeks	M&F	16	0.42	0.43	0.41	0.40*
	3 months	M&F	16	0.45	0.44(m)	0.42(m)	0.40(m)
	6 months	M&F	16	0.46	0.44(m)	0.41(m)	0.40(m)
	9 months	M&F	12	0.46	0.45	0.42*	0.43*
	12 months	M&F	12	0.46	0.46	0.43	0.43

RBC = erythrocytes (10^{-12}/l; Hb = haemoglobin (g/l); Ht = haematocrit
* = significantly different from the control ($p \leq 0.05$)
(m) = only males statistically significant;

Add-on 1-year feeding study in dogs

In view of the changes in liver and adrenal gland occurring in all treated groups during the first study a supplementary study was performed in order to establish a clear NOEL for these changes. (94.2 %) was administered to groups of Beagles (6 animals/sex/group) at dietary levels of 0 - 60 - 160 or 1600 ppm over a period of 1 year. These concentrations were equivalent to a mean daily substance intake (mg/kg body weight) of 0, 4.7, 11.8 and 125 (males) and 0, 4.5, 11.0 and 119 (females). This study included also special endocrinological parameters in order to elucidate more precisely the hormonal status of the adrenal gland and also of the male reproductive organs. In addition, adipose tissues were taken for residue determinations in view of the lipophilic nature of ; this part of the study is reported under section 1.4.

Food consumption was not impaired in any dosing group, whereas the body weight gains of the females from the high dose group showed a slight to marked decrease. One control male, one low dose female and two high-dose females had

ACTIVE SUBSTANCE:

POINT 5: INFORMATION ON TOXICOLOGY

type of study	diet	plateau concentration			elimination	reference
	(ppm)	time (month)	ppm	BCF	half-life (day)	
multigeneration rat, P dam	200	ND	718	**3.6**	ND	A519968
4-wk dermal toxicity rat	100 [A]	ND	53	0.5	27	A52888

- = no tissue taken; [A] = mg/kg b.w.; ND = not determined; [SC] = subcut. fat; [RP] = retroperitoneal fat;
* = calculated values;

Residues in fat were eliminated rapidly ($T_{1/2}$ = 4 - 8 days) after single dosing, but considerably more slowly ($T_{1/2}$ = 13 - 182 days) after repeated dosing. Plateaus were reached after 3 to 12 months during prolonged feeding. Elimination half-lives of 39 - 47 days were obtained in a chronic rat feeding study (5 mg/kg diet). The BCF values derived from chronic toxicity studies in different species were comparable and ranged from 3-5.

In the other organs and tissues only very low residue levels were found resulting in BCF values of much less than 0.1 (liver, kidneys, testes) and less than 0.01 (brain).

A detailed review of the toxicokinetic and metabolism studies is given in a document prepared by Stumpf 1995. A54407

5.1.6 Carcinogenicity

No carcinogenic effects were shown in either rats or mice see chronic toxicity.

5.1.6.1 Rat oral

See chronic toxicity above

5.1.6.2 Rat inhalation

Data not available

5.1.6.3 Other animal species oral

See chronic toxicity above

ACTIVE SUBSTANCE:

POINT 5: INFORMATION ON TOXICOLOGY

5.1.7 Mutagenicity

5.1.7.1 in-vitro

Gene mutation

Prokaryotes (Ames-Test)

(95.4%), dissolved in DMSO, was tested in Salmonella typhimurium TA 98, TA 100, TA 1535, and TA 1537 and in Escherichia coli WP2 uvrA for the potential to induce reverse gene mutations. The concentrations used ranged from 4 to 10000 µg/plate in the 1st experiment and from 4 to 10000 µg/plate in the 2nd experiment. At concentrations equal to or exceeding 2500 µg/plate, precipitation of the test material was noted. No mutagenic activity was noted either in the presence or in the absence of a rat liver derived activation system.

A36830

Mammalian cells - HGPRT-test in Chinese hamster V-79 cells

In the in vitro HGPRT-test using the Chinese hamster cell line V-79, no increased rate of mutation was detected either in the presence or in the absence of a rat liver S9 microsomal fraction in two independent experiments. The concentrations of (96.8%), dissolved in DMSO, tested ranged from 250 to 1000 µg/ml and were limited by the solubility of the test substance above 1000 µg/ml.

A38558

Chromosomal aberration

Cultured human lymphocytes

(96.8%) was dissolved in DMSO and tested in concentrations of 6.0, 60 and 160 µg/ml for its potential to induce structural chromosome aberrations in human lymphocytes in vitro. Preparation of chromosomes was done 24 h (all doses), and 48 h (highest dose) after the start of treatment (duration 4 h). In each experimental group two parallel cultures were used and 100 metaphases were scored per culture. Treatment of the cells with highest concentrations reduced the mitotic index at fixation interval 24 h in both the presence and absence of metabolic activation (liver S-9 mix) and 48 h with S9 mix. In this test induced no biologically relevant increases in aberrant cells in contrast to the positive reference substances used.

A40038, A40039, A42116

ACTIVE SUBSTANCE:

POINT 5: INFORMATION ON TOXICOLOGY

DNA-pertubation / damage

Prokaryotes - Rec assay in B. subtilis

(93.2%) was dissolved in DMSO and tested for differential toxicity in recombination repair proficient and repair-deficient strains of Bacillus subtilis (H17 and M45) in the absence and presence of an activation system at 5 doses between of 625 and 10000 µg/disk. did not produce a zone of killing up to 10000 µg/disk in either strain and was negative in the assay in contrast to the reference substances. was considered to have no potential of DNA damage under the conditions of this test.

A44855

Eukaryotes - Mitotic gene conversion in Saccharomyces cerevisiae (strain D4)

(96.8%) was dissolved in ethanol and tested in 6 concentrations ranging from 39 to 1250 µg/ml with and without metabolic activation for the induction of mitotic gene conversion in Saccharomyces cerevisiae (strain D4) in two independent experiments. The maximum dose level was the highest concentration which could be achieved in the assay medium without exceeding acceptable solvent concentrations. did not induce three-fold increases in the frequency of mitotic gene conversion and was not toxic to the test organism at any dose level in contrast to the positive reference substances used.

A39978, A42884

Mammalian cells - UDS-test in the mammalian cell line A549

(96.8%) was examined in the in vitro unscheduled DNA synthesis test (UDS-test) in the mammalian cell line A549 by excision repair in cells in culture. The test was performed in the presence and absence of metabolic activation (rat liver S-9 fraction). Two independent experiments with 7 concentration levels (range 1 to 2000 µg/ml) were carried out using DMSO as solvent. No relevant reproducible increase in unscheduled DNA synthesis was observed in any test with in contrast to the positive reference substances used in this test.

A38559

5.1.7.2 in-vivo

Micronucleus test in mice

In the mouse micronucleus test, (96.8%) was dissolved in sesame oil and administered orally to groups of 5 male and 5 female NMRI mice at a single dose of 1250, 2500 or 5000 mg/kg body weight. Evaluation of bone marrow smears (scoring of 1000 polychromatic erythrocytes per animal) obtained 24, 48 and 72 hours after dosing with did not demonstrate any increase in the incidence of micronuclei in contrast to the positive reference substance endoxan.

A38802

Bone marrow chromosome aberration assay in the Chinese hamster

(96.8%) was dissolved in paraffin oil and administered orally to groups of 5 male and 5 female Chinese hamsters at a single dose of 150, 500 or 1500 mg/kg body weight. The animals from the highest dose exhibited clinical signs in the form of apathy indicating that the maximum dose suitable for the test system had been reached. From each animal 50 well spread metaphases were scored for gaps, breaks, fragments, deletions, exchanges and chromosomal disintegrations. Evaluation of bone marrow smears obtained 24, 48 and 72 hours after dosing with did not demonstrate any increase in the chromosome aberration frequency in contrast to the positive reference substance cyclophosphamide.

A39670, A39671

5.1.8 Reproduction toxicity

5.1.8.1 Two generation study rat oral

Preliminary study

In a preliminary study to the two-generation reproduction study (96.1%) was administered at dietary concentrations of 0, 400, 2000 and 10000 ppm to groups of 10 male and 10 female Wistar rats during a 3-week pre-pairing period and throughout the pairing (maximum of 15 days), gestation and lactation periods. After weaning (day 21 post partum), the parents and F1 pups which were not selected for organ weight analysis were reared for a further week on the respective test diet. At 2000 and 10000 ppm, there was a reduction in food consumption in the females during the lactation period and a reduction in the mean number of implantation sites and pups per dam. At 10000 ppm, retardation of body weight gain was noted in the parents as well as in the pups; additionally, the food consumption of the pups was reduced from days 21 - 28 post partum. The parent males of this group showed markedly reduced weight of the testes (30%). Based on these results dosages of 200, 1000 and 5000 ppm (diet) were chosen for the main study.

A49556

			Dose (mg/ kg diet)			
Parameter	**Sex**	**No.**	**0**	**400**	**2000**	**10000**
Weight of male reproductive organs (%)						
Testes	M	10	0.97	0.94	0.93	0.68*
Litters	F	10	10	10	10	9
Implantations per dam	F	10	12.4	12.1	9.9	9.2*

Two-generation reproduction study in the rat

Study design : In a two-generation reproduction study (96.1%) was fed in the diet to groups of 25 male and 25 female rats in concentrations of 0 - 200 - 1000 or 5000/2000 ppm; due to reduced male fertility at 5000 ppm, this dose level was reduced to 2000 ppm at the beginning of the preparing period of the F1 generation. The animals received the test material over a period of 70 days prior to mating (F1A) and throughout gestation and lactation. The P generation were mated again to produce the F1B generation. During weaning of the F1B generation, pups were selected to deliver the F2A and F2B generations. Diet containing was fed to all animals of all generations.

In addition to this study design the following special tests were performed: After weaning of the F1 pups, 15 males and 15 females of the P generation in the control and 5000 ppm groups were selected for a "cross foster" pairing, i.e. 5000 ppm males were paired with control females and vice-versa; during this phase both groups received control diet. From the F1 parent males, blood samples were collected prior to necropsy for the determination testosterone and progesterone in the plasma.

In addition, deep frozen adipose tissue and plasma samples were preserved from selected parents and pups from both generations for residue examinations. From these plasma samples, testosterone and progesterone levels of the parent males of the P and also of the F1 generation (for verification) were determined. The results of the residue examinations in adipose tissue is reported under section 1.4.

Results :

General parental toxicity: Slight general toxicity was established from 2000 ppm onwards in the F1 parents and also in the 5000 ppm females (during lactation) of the P generation in the form of reduced food consumption. Clinical signs related to treatment were not observed at any stage of the study. With regard to parameters related to reproduction toxicity the following changes were noted :

Male and female fertility: At 5000 ppm (P generation) the number of pregnant females, the mean number of implantation sites per dam and the litter size were markedly reduced. The "cross foster" pairing indicated that this effect was due to reduced male fertility. This finding was confirmed by the reduced testes weight (18%) and by macroscopy (testes flaccid or reduced size in 16% of the males). Additionally, histopathology revealed atrophy of seminiferous tubules in the testes with concomitant reduction in spermatozoa and the presence of exfoliated seminiferous tubular epithelial cells in the epididymides.

At 1000 and 2000 ppm, increased plasma levels of progesterone were noted in the F1 males. However, in the absence of any corresponding change in the testosterone levels and taking into consideration that no impairment of male fertility occurred up to 2000 ppm, no toxicological relevance was assigned to this change. This judgement may be considered to be supported by the supplementary (re)examination of the deep frozen plasma samples (Burri, 1995): Selected males of the P generation with testicular lesions showed no changes in testosterone and progesterone and the verifying examinations of selected F1 males could not confirm the increase in progesterone as observed at the first measurement. Therefore, it can be concluded that no endrocrinological mechanism is involved in the impairment of male fertility.

Progeny : At 5000 ppm a slight impairment in body weight development was noted in the F1 pups during the lactation period; this effect must be seen in connection with the reduced food consumption of the dams. At 2000 ppm a slight increase of the number of dead pups at first litter check was noted in the F2B litters.

The No Adverse Observable Effect Level for the parent animals, for the reproduction data and for the progeny data was considered to be 1000 ppm, equivalent to a mean daily substance intake of 69.2 and 96.3 mg/kg body weight for the males and females, respectively.

The changes in male reproduction parameters are summarised in the table below:

A49487, A51275, A54529

P-Generation	**Diet concentration (ppm)**				
Parameter	No.	0	200	1000	5000
Testes weight (%)	25	0.85	0.92	0.91	0.70*
Pathology					
flaccid or reduced in size	25	/	/	/	4
SemTubAtroph	25	/	/	1	12
Epith vacuolation	25	/	/	/	8
Epididymides - Pathology					
ReducSperm	23 - 24	/	/	/	10
EpithAtroph	23 - 24	/	/	3	19
Male fertility - pregnant dams (% mated)					
Standard experiment	25	100	100	96	36*
HD males & control females	15	100			53*
Control males & HD females	15	100			100
Testosterone/ progesterone Burri 1995	4-5	1.4 / 7.8	1.4 / 5.0	3.3 / 7.8	3.8 / 4.5
F1-Generation	**Diet concentration (ppm)**				
Parameter	No.	0	200	1000	2000
Testes weight (%)	25		NS	NS	NS
SemTubAtroph	25	1	ND	ND	/
Epididymides					
ReducSperm	25	1	ND	ND	/
EpithAtroph	25	2	ND	ND	1
Testosterone (ng/ml)	25	0.95	0.9	1.16	0.78
verification by Burri 1995	3-5	1.45	ND	ND	ND

P-Generation	Diet concentration (ppm)				
Progesterone (ng/ml)	25	0.18	0.28	0.74*	0.97*
verification by Burri 1995	3-5	2.5	3.1	2.5	3.0

NS = not significantly different from control; * = stat. significant at $p \leq 0.05$;
/ = no finding; ND = not determined; HD = highest dose (5000 ppm)
SemTubAtroph = atrophy of seminiferous tubules;
ReducSperm = reduction in spermatozoa;
EpithAtroph = epithelial cell atrophy

5.1.9 Embryotoxicity, Teratogenicity

5.1.9.1 Rat oral

Oral route

(94.9%) was suspended in starch mucilage and administered in a limit test orally by gavage once daily from days 6 to day 16 of gestation to groups of 20 female Wistar rats at a dose level of 0 (vehicle control) or 1000 mg/kg body weight. The dams were killed and delivered by caesarean section on day 20 of gestation. The foetuses were then examined morphologically for developmental disturbances. Testing showed that treatment with had no harmful effect on the general condition of the dams or on the intrauterine development of the conceptuses. The morphological examination of the foetuses for stage of development, external anomalies and anomalies of the internal organs and skeleton provided no evidence of an embryotoxic or teratogenic potential of

Thus, the No Observed Effect Level in rats for maternal as well as developmental effects was 1000 mg/kg body weight.

A40312

Embryotoxicity and postnatal development

(93.2%) was suspended in starch mucilage and administered in a limit test orally by gavage once daily from days 6 to day 16 of gestation to groups of 20 female Wistar rats at a dose level of 0 (vehicle control) or 1000 mg/kg body weight. The dams were to deliver normally and rear their offspring for 21 days. During the rearing period the physical development and viability of the offspring were examined. After this all of the pups were subjected to function tests, and one

male and female pup per litter were also subjected to behaviour and activity tests. The study was terminated by autopsy of dams and offspring.

Testing showed that treatment with did not impair the general condition of the dams, interfere with the course of gravidity and delivery, or cause any disturbance of the intrauterine or post-natal development of the offspring.

The No Observed Effect Level for maternal toxicity, embryonic/foetal and post-natal toxicity in this study was 1000 mg/kg body weight.

A46834

5.1.9.2 **Other animal species**

Rabbit teratogenicity - Oral route

1st study: (94.9%) was mixed with starch mucilage and administered in a limit test orally by gavage once daily from days 6 to day 18 of gravidity to groups of 15 female Himalayan rabbits at a dose level of 0 (vehicle control) or 1000 mg/kg body weight. The dams were killed and delivered by caesarean section on day 29 of gravidity. The foetuses were kept for 24 hours in an incubator as a viability check and then examined morphologically for developmental disturbances.

Testing showed that treatment with caused a slight reduction of food consumption of the dams during the treatment and an increased incidence of intrauterine deaths. The live foetuses at delivery were normally developed in outward appearance and showed no impairment of viability during the first 24 hours. Morphological examination indicated a slight embryotoxic effect in the form of increased incidences of a 13th rib in the treated group, but there was no evidence for any teratogenic potential of

The No Observed Effect Level in rabbits for maternal as well as developmental effects was considered to be less than 1000 mg/kg body weight.

A40311

Add-on study : As a follow up of above reported Limit test with a dose of 1000 mg/kg body weight, (94.9%) was mixed with starch mucilage and administered in a orally by gavage once daily from days 6 to day 18 of gravidity to groups of 15 female Himalayan rabbits at a dose level of 0 (vehicle control), 100 or 300 mg/kg body weight. The dams were killed and delivered by caesarean section on day 29 of gravidity. The foetuses were kept for 24 hours in an incubator as a viability check and then examined morphologically for developmental disturbances.

Testing showed that treatment with at doses up to and including 300 mg/kg body weight had no harmful effect on the general condition of the dams or on the intrauterine development of the conceptuses. The viability of the foetuses during the first 24 hours in the incubator also remained unaffected. The morphological examination of the foetuses for stage of development, external anomalies and anomalies of the internal organs and skeleton provided no evidence of an embryotoxic or teratogenic potential of

Thus, the No Observed Effect Level in rabbits for maternal as well as developmental effects was 300 mg/kg body weight.

3 INFORMATION ABOUT THE ACTIVE INGREDIENT

3.1 Name of the manufacturer

Hoechst Schering AgrEvo GmbH
D-65926 Frankfurt am Main
Federal Republic of Germany

3.1.1 Common name

3.1.2 Chemical name (IUPAC)

3.1.3 CAS number

3.1.4 Molecular mass

3.1.5 Empirical formula

3.1.6 Structural formula

CONFIDENTIAL

3.2 Type of active ingredient

non-ester pyrethroid - sodium channel blocker

3.2.1 Use

Insecticide for control of Coleoptera, Diptera, Heteroptera, Homoptera, Isoptera, Lepidoptera, Orthoptera and Thysanoptera.

ACTIVE SUBSTANCE:

POINT 3: INFORMATION ABOUT THE ACTIVE INGREDIENT

3.2.2 **Mode of action**

A broad-spectrum insecticide which acts mainly as a stomach poison, but also by contact.

3.3 **Melting point**

not relevant

3.4 **Boiling point**

Not determinable

3.5 **Density**

1.08 ± 0.05 g/cm³ at 293 K (20 °C) A43077

3.6 **Vapor pressure**

2.5×10^{-6} Pa at 20°C

5.5×10^{-6} Pa at 25°C

1.9×10^{-4} Pa at 50°C A40002

3.7 **Solubility**

3.7.1 **Solubility in water**

1 µg/l (20 °C) A41447

3.7.2 **Solubility in organic solvents**

Solubility of technical at 20°C	
Solvent	**g/l**
n-hexane	> 300
toluene	> 300
dichloromethane	> 300
acetone	> 300
ethyl acetate	> 300
dimethylsulfoxide	> 300
isopropanol	> 300
methanol	118
PEG	> 300

A40028

ACTIVE SUBSTANCE:

POINT 3: INFORMATION ABOUT THE ACTIVE INGREDIENT

3.8 **Partition coefficient n-octanol/water**

Partition Coefficient log P: 8.2 A43166

3.9 **Purity of the technical active ingredient**

min. 91 % A49606

ACTIVE SUBSTANCE:

POINT 3: INFORMATION ABOUT THE ACTIVE INGREDIENT

3.10

CONFIDENTIAL

ACTIVE SUBSTANCE:

POINT 3: INFORMATION ABOUT THE ACTIVE INGREDIENT

3.11 Stability under chemical influences

3.11.1 Dissociation constant

has neither acidic nor basic functional groups. Dissociation, if any is expected to be negligible. Therefore, quoting a value for the dissociation constant for does not appear meaningful. A45954

3.11.2 Hydrolysis rate

Abiotic hydrolysis at 25 °C:		
pH value	mean mass balance (%)	half live (days)
5	93.3	> 365
7	87.1	> 365
9	86.4	> 365

A50651

3.12 Stability under irradiation

3.12.1 UV spectrum

Please refer to Document

3.12.2 Quantum yield

Not applicable

3.12.3 Indirect photochemical degradation

Photodegradation on soil:

Assuming first order kinetics, the extrapolated half-life for the photodegradation of was calculated as 885 days and -2,837days, thus indicating that within the rage of deviation no significant photolytic breakdown occurred. A52838

3.13 Stability to special physical effects

Not applicable

DNA-pertubation / damage

Prokaryotes - Rec assay in B. subtilis

(93.2%) was dissolved in DMSO and tested for differential toxicity in recombination repair proficient and repair-deficient strains of Bacillus subtilis (H17 and M45) in the absence and presence of an activation system at 5 doses between of 625 and 10000 µg/disk. did not produce a zone of killing up to 10000 µg/disk in either strain and was negative in the assay in contrast to the reference substances. was considered to have no potential of DNA damage under the conditions of this test.

A44855

Eukaryotes - Mitotic gene conversion in Saccharomyces cerevisiae (strain D4)

(96.8%) was dissolved in ethanol and tested in 6 concentrations ranging from 39 to 1250 µg/ml with and without metabolic activation for the induction of mitotic gene conversion in Saccharomyces cerevisiae (strain D4) in two independent experiments. The maximum dose level was the highest concentration which could be achieved in the assay medium without exceeding acceptable solvent concentrations. did not induce three-fold increases in the frequency of mitotic gene conversion and was not toxic to the test organism at any dose level in contrast to the positive reference substances used.

A39978, A42884

Mammalian cells - UDS-test in the mammalian cell line A549

(96.8%) was examined in the in vitro unscheduled DNA synthesis test (UDS-test) in the mammalian cell line A549 by excision repair in cells in culture. The test was performed in the presence and absence of metabolic activation (rat liver S-9 fraction). Two independent experiments with 7 concentration levels (range 1 to 2000 µg/ml) were carried out using DMSO as solvent. No relevant reproducible increase in unscheduled DNA synthesis was observed in any test with in contrast to the positive reference substances used in this test.

A38559

ACTIVE SUBSTANCE:

POINT 5: INFORMATION ON TOXICOLOGY

In addition to this study design the following special tests were performed: After weaning of the F1 pups, 15 males and 15 females of the P generation in the control and 5000 ppm groups were selected for a "cross foster" pairing, i.e. 5000 ppm males were paired with control females and vice-versa; during this phase both groups received control diet. From the F1 parent males, blood samples were collected prior to necropsy for the determination testosterone and progesterone in the plasma.

In addition, deep frozen adipose tissue and plasma samples were preserved from selected parents and pups from both generations for residue examinations. From these plasma samples, testosterone and progesterone levels of the parent males of the P and also of the F1 generation (for verification) were determined. The results of the residue examinations in adipose tissue is reported under section 1.4.

Results :

General parental toxicity: Slight general toxicity was established from 2000 ppm onwards in the F1 parents and also in the 5000 ppm females (during lactation) of the P generation in the form of reduced food consumption. Clinical signs related to treatment were not observed at any stage of the study. With regard to parameters related to reproduction toxicity the following changes were noted :

Male and female fertility: At 5000 ppm (P generation) the number of pregnant females, the mean number of implantation sites per dam and the litter size were markedly reduced. The "cross foster" pairing indicated that this effect was due to reduced male fertility. This finding was confirmed by the reduced testes weight (18%) and by macroscopy (testes flaccid or reduced size in 16% of the males). Additionally, histopathology revealed atrophy of seminiferous tubules in the testes with concomitant reduction in spermatozoa and the presence of exfoliated seminiferous tubular epithelial cells in the epididymides.

At 1000 and 2000 ppm, increased plasma levels of progesterone were noted in the F1 males. However, in the absence of any corresponding change in the testosterone levels and taking into consideration that no impairment of male fertility occurred up to 2000 ppm, no toxicological relevance was assigned to this change. This judgement may be considered to be supported by the supplementary (re)examination of the deep frozen plasma samples (Burri, 1995): Selected males of the P generation with testicular lesions showed no changes in testosterone and progesterone and the verifying examinations of selected F1 males could not confirm the increase in progesterone as observed at the first measurement. Therefore, it can be concluded that no endrocrinological mechanism is involved in the impairment of male fertility.

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Progeny : At 5000 ppm a slight impairment in body weight development was noted in the F1 pups during the lactation period; this effect must be seen in connection with the reduced food consumption of the dams. At 2000 ppm a slight increase of the number of dead pups at first litter check was noted in the F2B litters.

The No Adverse Observable Effect Level for the parent animals, for the reproduction data and for the progeny data was considered to be 1000 ppm, equivalent to a mean daily substance intake of 69.2 and 96.3 mg/kg body weight for the males and females, respectively.

The changes in male reproduction parameters are summarised in the table below:

A49487, A51275, A54529

P-Generation	**Diet concentration (ppm)**				
Parameter	No.	0	200	1000	5000
Testes weight (%)	25	0.85	0.92	0.91	0.70*
Pathology					
flaccid or reduced in size	25	/	/	/	4
SemTubAtroph	25	/	/	1	12
Epith vacuolation	25	/	/	/	8
Epididymides - Pathology					
ReducSperm	23 - 24	/	/	/	10
EpithAtroph	23 - 24	/	/	3	19
Male fertility - pregnant dams (% mated)					
Standard experiment	25	100	100	96	36*
HD males & control females	15	100			53*
Control males & HD females	15	100			100
Testosterone/ progesterone Burri 1995	4-5	1.4 / 7.8	1.4 / 5.0	3.3 / 7.8	3.8 / 4.5
F1-Generation	**Diet concentration (ppm)**				
Parameter	No.	0	200	1000	2000
Testes weight (%)	25		NS	NS	NS
SemTubAtroph	25	1	ND	ND	/
Epididymides					
ReducSperm	25	1	ND	ND	/
EpithAtroph	25	2	ND	ND	1
Testosterone (ng/ml)	25	0.95	0.9	1.16	0.78
verification by Burri 1995	3-5	1.45	ND	ND	ND

male and female pup per litter were also subjected to behaviour and activity tests. The study was terminated by autopsy of dams and offspring.

Testing showed that treatment with did not impair the general condition of the dams, interfere with the course of gravidity and delivery, or cause any disturbance of the intrauterine or post-natal development of the offspring.

The No Observed Effect Level for maternal toxicity, embryonic/foetal and post-natal toxicity in this study was 1000 mg/kg body weight.

A46834

5.1.7.2 in-vivo

Micronucleus test in mice

In the mouse micronucleus test, (96.8%) was dissolved in sesame oil and administered orally to groups of 5 male and 5 female NMRI mice at a single dose of 1250, 2500 or 5000 mg/kg body weight. Evaluation of bone marrow smears (scoring of 1000 polychromatic erythrocytes per animal) obtained 24, 48 and 72 hours after dosing with did not demonstrate any increase in the incidence of micronuclei in contrast to the positive reference substance endoxan.

A38802

Bone marrow chromosome aberration assay in the Chinese hamster

(96.8%) was dissolved in paraffin oil and administered orally to groups of 5 male and 5 female Chinese hamsters at a single dose of 150, 500 or 1500 mg/kg body weight. The animals from the highest dose exhibited clinical signs in the form of apathy indicating that the maximum dose suitable for the test system had been reached. From each animal 50 well spread metaphases were scored for gaps, breaks, fragments, deletions, exchanges and chromosomal disintegrations. Evaluation of bone marrow smears obtained 24, 48 and 72 hours after dosing with did not demonstrate any increase in the chromosome aberration frequency in contrast to the positive reference substance cyclophosphamide.

A39670, A39671

5.1.8 Reproduction toxicity

5.1.8.1 Two generation study rat oral

Preliminary study

In a preliminary study to the two-generation reproduction study (96.1%) was administered at dietary concentrations of 0, 400, 2000 and 10000 ppm to groups of 10 male and 10 female Wistar rats during a 3-week pre-pairing period and throughout the pairing (maximum of 15 days), gestation and lactation periods. After weaning (day 21 post partum), the parents and F1 pups which were not selected for organ weight analysis were reared for a further week on the respective test diet. At 2000 and 10000 ppm, there was a reduction in food consumption in the females during the lactation period and a reduction in the mean number of implantation sites and pups per dam. At 10000 ppm, retardation of body weight gain was noted in the parents as well as in the pups; additionally, the food consumption of the pups was reduced from days 21 - 28 post partum. The parent males of this group showed markedly reduced weight of the testes (30%). Based on these results dosages of 200, 1000 and 5000 ppm (diet) were chosen for the main study.

A49556

			Dose (mg/ kg diet)			
Parameter	**Sex**	**No.**	**0**	**400**	**2000**	**10000**
Weight of male reproductive organs (%)						
Testes	M	10	0.97	0.94	0.93	0.68*
Litters	F	10	10	10	10	9
Implantations per dam	F	10	12.4	12.1	9.9	9.2*

Two-generation reproduction study in the rat

Study design : In a two-generation reproduction study (96.1%) was fed in the diet to groups of 25 male and 25 female rats in concentrations of 0 - 200 - 1000 or 5000/2000 ppm; due to reduced male fertility at 5000 ppm, this dose level was reduced to 2000 ppm at the beginning of the preparing period of the F1 generation. The animals received the test material over a period of 70 days prior to mating (F1A) and throughout gestation and lactation. The P generation were mated again to produce the F1B generation. During weaning of the F1B generation, pups were selected to deliver the F2A and F2B generations. Diet containing was fed to all animals of all generations.

P-Generation	Diet concentration (ppm)				
Progesterone (ng/ml)	25	0.18	0.28	0.74*	0.97*
verification by Burri 1995	3-5	2.5	3.1	2.5	3.0
NS = not significantly different from control; * = stat. significant at $p \leq 0.05$; / = no finding; ND = not determined; HD = highest dose (5000 ppm) SemTubAtroph = atrophy of seminiferous tubules; ReducSperm = reduction in spermatozoa; EpithAtroph = epithelial cell atrophy					

5.1.9 Embryotoxicity, Teratogenicity

5.1.9.1 Rat oral

Oral route

(94.9%) was suspended in starch mucilage and administered in a limit test orally by gavage once daily from days 6 to day 16 of gestation to groups of 20 female Wistar rats at a dose level of 0 (vehicle control) or 1000 mg/kg body weight. The dams were killed and delivered by caesarean section on day 20 of gestation. The foetuses were then examined morphologically for developmental disturbances. Testing showed that treatment with had no harmful effect on the general condition of the dams or on the intrauterine development of the conceptuses. The morphological examination of the foetuses for stage of development, external anomalies and anomalies of the internal organs and skeleton provided no evidence of an embryotoxic or teratogenic potential of

Thus, the No Observed Effect Level in rats for maternal as well as developmental effects was 1000 mg/kg body weight.

A40312

Embryotoxicity and postnatal development

(93.2%) was suspended in starch mucilage and administered in a limit test orally by gavage once daily from days 6 to day 16 of gestation to groups of 20 female Wistar rats at a dose level of 0 (vehicle control) or 1000 mg/kg body weight. The dams were to deliver normally and rear their offspring for 21 days. During the rearing period the physical development and viability of the offspring were examined. After this all of the pups were subjected to function tests, and one

5.1.9.2 **Other animal species**

Rabbit teratogenicity - Oral route

1st study: (94.9%) was mixed with starch mucilage and administered in a limit test orally by gavage once daily from days 6 to day 18 of gravidity to groups of 15 female Himalayan rabbits at a dose level of 0 (vehicle control) or 1000 mg/kg body weight. The dams were killed and delivered by caesarean section on day 29 of gravidity. The foetuses were kept for 24 hours in an incubator as a viability check and then examined morphologically for developmental disturbances.

Testing showed that treatment with caused a slight reduction of food consumption of the dams during the treatment and an increased incidence of intrauterine deaths. The live foetuses at delivery were normally developed in outward appearance and showed no impairment of viability during the first 24 hours. Morphological examination indicated a slight embryotoxic effect in the form of increased incidences of a 13th rib in the treated group, but there was no evidence for any teratogenic potential of

The No Observed Effect Level in rabbits for maternal as well as developmental effects was considered to be less than 1000 mg/kg body weight.

A40311

Add-on study: As a follow up of above reported Limit test with a dose of 1000 mg/kg body weight, (94.9%) was mixed with starch mucilage and administered in a orally by gavage once daily from days 6 to day 18 of gravidity to groups of 15 female Himalayan rabbits at a dose level of 0 (vehicle control), 100 or 300 mg/kg body weight. The dams were killed and delivered by caesarean section on day 29 of gravidity. The foetuses were kept for 24 hours in an incubator as a viability check and then examined morphologically for developmental disturbances.

Testing showed that treatment with at doses up to and including 300 mg/kg body weight had no harmful effect on the general condition of the dams or on the intrauterine development of the conceptuses. The viability of the foetuses during the first 24 hours in the incubator also remained unaffected. The morphological examination of the foetuses for stage of development, external anomalies and anomalies of the internal organs and skeleton provided no evidence of an embryotoxic or teratogenic potential of

Thus, the No Observed Effect Level in rabbits for maternal as well as developmental effects was 300 mg/kg body weight.

A44205

5.1.10 **Special toxicity studies**

Acute delayed neurotoxicity in adult hens

(96.8 %), as original, was administered twice orally at the limit dose of 5000 mg/kg body weight to 12 White Leghorn hens, with an interval of 21 days between each application. A negative control (sesame oil, 4.6 ml/kg body weight) and a positive control (TOCP, 500 mg/kg body weight), each composed of 6 hens, were also included in the study. The neurotoxicity study was preceded by an acute oral toxicity study of the test substance (LD_{50}).

After treatment with the test substance no clinical signs of intoxication were observed and all hens survived until the end of the study. No clinical signs of delayed neurotoxicity in the form of ataxia could be established. Histopathological examination of brain, spinal cord and peripheral nerves indicated no pathomorphological lesions. In contrast, the hens in the positive control group (TOCP) showed the typical neurotoxic effects produced by this reference substance in the form of prolonged delayed-onset severe ataxia or, in some of the animals, paralysis, together with pathomorphological lesions especially in the form of damage to myelinised nerve fibres. These lesions were strongly marked in the substantia alba of all segments of the spinal cord, and less pronounced in the tractus spinocerebellaris of the medulla oblongata; microscopic examination showed them to be axonal swellings. Based on these results was considered to cause no Organophosporus Induced Delayed Neurotoxicity (OPIDN) at the maximum recommended dose level of 5000 mg/kg body weight.

A45316

5.1.11 **Publications about toxicology of the active ingredient**

Data not available.

ACTIVE SUBSTANCE:

POINT 5: INFORMATION ON TOXICOLOGY

5.2 **Acute toxicity of the formulated product**

Please refer to the file on the Products submitted by the Weyl Company.

5.2.1 **Rat oral**

See above

5.2.2 **Rat dermal**

See above

5.2.3 **Rat inhalation**

See above

5.2.4 **Rabbit skin irritation**

See above

5.2.5 **Rabbit eye irritation**

See above

ACTIVE SUBSTANCE:

POINT 6: INFORMATION ON RELEASE OF THE ACTIVE INGREDIENT INTO THE ENVIRONMENT

6 INFORMATION ON RELEASE OF THE ACTIVE INGREDIENT INTO THE ENVIRONMENT

The release of the active substance into the environment on the properties of the active substance in the formulation (water soluble concentrate) and also dependent on the envisaged use pattern. The application areas of the product to be considered will cover risk classification 1 to 3 (according to DIN 68800). Application restrictions will be imposed for

- wood which may come into direct contact with food or animal feeding stuffs
- >extensive building components of wood [surface to volume ratio equal to or greater than 0.2 (m^2/m^3)] inside or as delimitation of rooms intended as permanent quarters for humans or animals or as storage areas for food or animal feeding stuffs.

The only permitted application technique will be vacuum pressure impregnation (VPI). Brushing, spraying (mistblowing), dipping and tank immersion will not be permitted.

To prevent leaching immediately after the impregnation process the wood must be protected against rain for a minimum time of 24 h.

6.1 Release in the air

To investigate the release of the active substance into the air (evaporation rate/air concentration) a model study was performed (EMPA, 1994, Doc. No.: A53081) using a microchamber with an internal volume of 1790 cm^3. A 20 cm^2 area on the surface of a wood sample (type of wood: deal, sapwood) was treated, resulting in a surface to volume ratio of ≈ 1.1 (m^2/m^3). The air flow (synthetic air, 20°C, 44% relative humidity) was adjusted to give an air turnover rate of 1 h^{-1}. The emission of was investigated over a period of 29 days.

The study was conducted following a design in agreement with BGVV (Dr. Westphal).

was applied at a rate of 568 mg per m^2. The active substance was applied as 0.15 % LOSP formulation „Defence Anti Insect Sila" (Ref. No. 93042)

After the application (duration: 85 min) the wooden block was dried at 25°C and 35% rH for 90 min. Sampling was performed by adsorption on Tenax adsorption tubes consisting of a n adsorbing and retarding layer. Sampling intervals in the first week were alternatively 2 and 20 h respectively, starting with a two-hour interval immediately after the wood had been placed in the microchamber (start of emission subsequently. On days 14 to 12, 21 to 22 and 28 to 29, sampling was

done in 20 h intervals. Furthermore a long-term sampling was performed from day 8 to day 14 over a 146 h interval.

Table 1: Results of EMPA trial

[application of 568 mg spruce wood; air turnover rate 1 h^{-1}; surface to volume ratio ≈ 1.1 (m^2/m^3); carrier gas synthetic air, 20°C, 44% rH]

days after application	sampling interval [h]	concentration in carrier gas [ng m^{-3}]	emission from wood [ng m^{-2} h^{-1}]
0	2	106	95
0-1	20	3.9	3.5
1-2	20	0.8	0.8
8 - 14	146	1.1	1.0
27-28	21	2.6	2.4

6.1.1 Maximum diffusion rate

A maximum evaporation rate of 95 ng m^{-2} h^{-1} could be calculated from the measured air concentration of the active substance during the first two hours. It should be noted in this connection, however, that there is a possibility with the first sampling interval, that very small amounts of wood-dust containing active substance may be transported by the carrier gas from the emission source to the adsorption tube. This is probably the reason why a rather high substance release via the gas phase was recorded, especially for the first sampling interval. During this period small particles of treated wood dust may have been transported by the transport gas from the source of emission to the adsorption tube.

A realistic estimate of the evaporation rate can be deduced from the measurements from day 1 to day 28 with evaporation rates between 0.8 and 3.5 ng m^{-2} h^{-1}.

6.1.2 Concentration expected indoors in the air of a room

The measured air concentrations within these trials can be taken as a direct estimate of an indoor air concentration under worst case conditions (surface to volume ratio of ≈ 1.1 m^2/m^3, air turnover rate of 1 h^{-1}, air temperature 20°C, relative humidity 44%).

A maximum concentration of of 106 ng m^{-3} was measured at the very beginning of the trial (first two hours). This value is of no relevance in view of the envisaged use pattern: in the case of the vacuum pressure impregnation the treated wood is kept at the manufacturer for at least 24 h for leaching protection (cf. 6).

The estimated rate of evaporation from treated wood surfaces should therefore be more orientated to the values for "aged "samples of day 1 to 28. Thus an indoor concentration of about 2 ng m^{-3} (span between 0.8 and 3.9 ng m^{-3}) over a 28 day time period can be expected.

These experimental values are well below the saturation concentration for in air (420 ng/m^3), an approximate value obtained on the basis of the vapour pressure of (Grewer, 1988, Doc. No.: A40002.)

6.1.3 Evaporation of the active ingredient caused by the solvent

The evaporation trials were conducted with a 0.15 % LOSP formulation (cf. 6.1.1).

6.2 Release into soil or water

No study was presented from which a direct leaching rate can be derived.

Indirect hints possibly can be concluded from efficacy trials with an accelerated ageing of the wood according to EN 84 (leaching procedure), where the efficacy of the test formulation results gave no evidence for any leaching of the active substance from treated wood samples. Active substance contents in the leachates were not analysed (ÖHFI, 1993)

A direct release into the soil compartment is not relevant because no application according to risk classification 4 of (wood with steady soil contact) is intended.

6.2.1 Maximum leaching rate

See above.

6.2.1.1 in fresh water

See above.

6.2.1.2 in ocean water

See above.

6.3 Reactions that can change the rate of release

No reactions known.

7 BEHAVIOR OF THE ACTIVE INGREDIENT IN THE ENVIRONMENT

7.1 Behavior in soil

7.1.1 Degradation and metabolism in soil

Aerobic soil metabolism:

The fate of the active substance was investigated in four soils (sandy loam, sand, loamy sand and a silt loam) under aerobic conditions at a temperature of 20 ± 2°C. The substance was applied onto the soil at a rate of 300 g/ha (0.4 mg/kg soil) and incubated up to 128 days.

Sampling of two replicates of each soil was done on days 4 (6), 8 (9), 16, (31) 32, (48) 49, 64, 80 and 128 (values in brackets are times for the loamy sand samples). The material balance for the end of the experiment (day 128) is summarized in **Table I.**

Table I: Material balance for degradation of in four soils at the end of the experiment (day 128 after application)

Soil	Volatiles ** [%]*	Extractables [%]*	Non-extractable Residues [%]*	Recovery*** [%]*
Sandy loam	10.4	29.3	43.1	82.7
Sand	3.3	37.0	41.7	82.2
Loamy sand	9.4	56.0	22.4	87.9
Silt loam	13.7	31.3	40.1	85.1

* all values given in % of total applied radioactivity, mean value of two replicates

** other volatiles than $^{14}CO_2$ were detected to < 0.4 %

*** poor recoveries may result from adsorption of to glass surfaces due to high log P_{ow}

Between 29 % (sandy loam) and 56 % (loamy sand) of total applied radioactivity were still extractable on day 128. Slow mineralisation was detected for the sand (3 %) increasing to moderate rates (14 %) for the silt loam. The main portion of extractable radioactivity consisted of unchanged parent compound (81 to 100 %). At least three metabolites were observed in a total of < 17 % (< 0.07 mg/kg)

during the incubation period. Identification was not feasible due to the low concentration and their inconsistent appearance in the course of the study. Consequently, a degradation scheme cannot be presented. On the other hand, degradation products showed no tendency for an accumulation in soil. The initial step of breakdown sequence must therefore be assumed as the slowest which is then followed by a rapid degradation of the metabolites.

DT_{50} and DT_{90} values[1)] were calculated assuming a first order kinetics and are shown in **Table II** for the individual soils.

Table II: Half-lives of in soils under aerobic conditions

Soil	DT_{50} [days]	DT_{90} [days]
Sandy loam	72	237
Sand	91	303
Loamy sand	148	490
Silt loam	85	281

It was therefore demonstrated that is finally mineralised under aerobic conditions (Schwab, 1992, Doc. No.: A49193).

Anaerobic degradation:

Phenoxy-UL-^{14}C-labelled was applied to a sandy loam soil at an application rate of 300 g/ha (0.4 mg/kg soil) and at 20 ± 2°C. After an aerobic starting and ageing phase for 30 days, conditions were converted to anaerobics by flooding the samples with water and purging the atmosphere above the samples with nitrogen. After establishment of anaerobic conditions (day 48, 18 days after flooding), further samples were collected on days 78, 108 and 143 after application (e.g. day 0, 30, 60 and 95 of anaerobic phase).

During the incubation period, extractability from soil remained nearly constant with a slow decrease from 95.8 % (day of application) to 76.4 - 83.0 % at the end of the study (day 143). Consequently, slow formation of $^{14}CO_2$ was observed accounting for 3.1 % on day 143. Other volatile degradation products were detected to < 0.1 % of total applied radioactivity. Non-extractable residues

[1)] DT_{50}: disappearance time of 50 % extractable parent compound
DT_{90}: disappearance time of 90 % extractable parent compound

increased from 0.4 % (day 0) to 7.5 - 13.3 % on day 143. No noticeable metabolite was detected, therefore the active substance was the relevant extractable residue.

A half-life time for dissipation of the anaerobic phase cannot be given, as no decrease of the concentration of in soil was observed under anaerobic conditions.

On the other hand, very low amounts of radioactivity were desorbed from soil particles. 0.5 - 3.5 % of total applied radiolabel were measured in the water phase after flooding (Schwab, 1992, Doc. No.: A49300).

The marginal desorption of from soil particles will thus not lead to high concentrations of the test substance in water even after a heavy rainfall event when assuming a runoff of soil into an aquatic ecosystem.

Aerobic aquatic metabolism:

The degradation of was studied under aerobic conditions in two sediment/water systems (a silt loam, "Nidda", and a sand, "Schwanheim") at 20 ± 2°C. Application was done on the basis of 0.124 kg a.s.[2]/ha water surface with sampling intervals on days 0, 3, 7, 14, 30, 92, 120, 182 and 241.

0.4 % (silt loam sediment) and 3 % (sand) of radiolabel applied were still present in the water phase on day 241 after application. At the same time, extractability from the sediments decreased constantly to approx. 19 - 24 % for the silt loam and 8 to 16 % for the sand sediment. Non-extractable residues were detected to 36 % (silt loam) and 47 - 54 % for the sand. 24 - 26 % of the radiolabel were found mineralised in the silt loam, 22 - 24 % in the sand system.

Other degradation products (nine in total) were observed in small percentages (each < 7 % of total applied radioactivity) during the incubation period.

By assuming a first order kinetics, the following half-lives were calculated which are presented in **Table III.**

Table III: DT_{50} and DT_{90} values for dissipation of in two sediment/water systems

Water / sediment system	DT_{50} [days]	DT_{90} [days]	DT_{50} [days]	DT_{90} [days]	DT_{50} [days]	DT_{90} [days]
	water		sediment		water/sediment	
Silt loam ("Nidda")	14.4*	47.7*	120.7	401.0	110.7	367.8

[2] a.s.: active substance

Sand ("Schwanheim")	1.4	4.5	100.1	332.6	84.4	280.4

*as a result of a check of data in the original report, adsorption of to the sediment is at least as fast as for the sand. Due to an error in calculation of dissipation times, higher values were reported. An amendment to this report is in preparation.

is rapidly eliminated from the water phase to the sediment, where the compound is finally mineralised. As no degradation products accumulated in the course of the study, the first step in degradation can be again assumed as the slowest process (Schwab, 1992, Doc. No. A49239).

As the dissipation of from the water phase is fast, no long term exposure of aquatic organisms to the parent compound is likely to occur (for more details see also chapter 8).

7.1.2 Adsorption / Desorption

(according to OECD Guideline 106). In addition, data on leaching, if available

A detailed study on the adsorption / desorption behaviour to soils was not carried out. From the high octanol/water coefficient (chapter 3.8), it must be concluded that a strong adsorption of the compound to organic matter of soil can be expected. An estimation of the K_{OC} value based on the octanol/water partition coefficient was made by Görlitz (1991, Doc. No.: A46678) and resulted in a K_{OC} of 10^8. Thus the compound has no leaching potential which is also underlined by a leaching study summarized below.

Column leaching:

The leaching potential of non-aged and aged (90 days) , formulated as , was investigated in three german standard soils 2.1, 2.2 and 2.3 (corresponding to a sand, loamy sand and sandy loam). Following an application rate of 300 g/ha and an (extreme) irrigation rate corresponding to 200 mm rain over 48 hours, between 0.41 and 1.14 % of radiolabel were detected in the leachates for non-aged samples. For aged samples, an average of 0.75 % (maximum value: 0.86 %) was determined under the same conditions. Neither nor its degradation products thus show a mobility and they must be considered as immobile in soil (Buettner, 1990, Doc. No. A44748).

is not intended for use on wood/timber which is in a steady contact to water. Due to a general tight binding of the compound to organic matter (lignine/cellulose particles of wood), leaching from treated wood is unlikely to occur, especially if the wood is moistened only occasionally in a rainfall event.

For this case, only a very minor release of active substance to compartments of the environment (water and/or soil) is likely to occur.

7.2 Behavior in water

Not relevant, as the formulated material will not be used for timber in a steady contact with water.

7.2.1 Degradation and metabolism

See above

7.2.2 Adsorption / desorption in sediment

See above

7.3 Bioaccumulation

The bioconcentration and successive depuration of in fish was conducted with bluegill sunfish (Lepomis macrochirus) in a dynamic study for a total of 70 days.

During an uptake period of 28 days, a flow-through system maintained an average concentration of 1.85 µg a.s./L water. This was followed by a 42 day depuration phase in clean water.

Bioconcentration factors (BCF) were determined for the whole fish as well as for edible and non-edible parts on days 0, 1, 3, 7, 14, 21 and 28 of the uptake phase. Five fish were sacrificed at each date, three were separated into edible/non-edible parts and two were taken as a whole for the analysis as a complete fish. During the depuration period, sampling was made on days 1, 3, 7, 10, 14, 17, 21, 28, 35 and 42. With the exception on days 17, 21, 28 and 35 (only two fish), three fish were investigated at each timepoint for edibles/non-edibles. Whole fish samples were analysed in duplicate until day 14 and, up to the end of the study, one fish was sampled during the depuration. For investigation of metabolism, 15 further fish were collected during the uptake on days 3 and 21.

A plateau concentration of radioactivity was reached between day 20 and 28. On day 28, concentration in the tissue of edible parts (fillet body, muscle, skin and skeleton) had increased to 0.769 mg a.s. equiv./kg fish. For non-edible parts (head, fins, viscera), 3.235 mg a.s. equiv./kg fish were determined. Finally, for the whole fish a concentration of 1.601 mg a.s. equiv./kg fish was found. Daily bioconcentration factors were determined to 411 for edibles and 1728 for non-edible parts on day 28, whereas for the whole fish a factor of 905 was calculated on day 21.

Elimination of the compound takes place on a moderate level with half-life times of 30 to 40 days.

Besides three minor degradation products (total: 9 % of radiolabel applied) was identified as the only relevant radioactive residue in non-edible tissues. For edible parts, unchanged parent compound was found as the only component.

The low water solubility (1 µg/L) and the high octanol/water partition coefficient (log P_{ow} 8.2) may have suggested an even higher bioconcentration factor (BCF). However, slow accumulation of in fish was observed reaching its highest BCF value of 1728 for non-edible parts only, whereas for the whole test organism a BCF of 905 was determined (Buettner and Fischer, 1988, Doc. No.: A40437).

8 DATA ON THE ECOTOXICOLOGICAL EFFECTS OF THE ACTIVE INGREDIENT

8.1 Toxicity for aquatic organisms

, substance technical, is not acute toxic to fish and green alga, even far above the water solubility, but is highly toxic to aquatic invertebrates.

The following results were obtained with the technical substance:

Test organism	Test design	Test method	LC/EC_{50} (mg/L)	NOEC (mg/L)	Reference
Scenedesmus subspicatus (green alga)	growth inhibition test 72 hours	OECD	>1000	1000	Fischer (1990a) Doc. No.: A43486)
Daphnia magna (water flea)	static acute test 48 hours	OECD	0.004	0.00018	Fischer (1987) Doc. No.: A44380
Daphnia magna (water flea)	reproduction test 21 days	OECD	n.r.	0.000056	Heusel (1992) Doc. No.: A49194
Palaemon aucidens (freshwater shrimp)	flow-through 96 hours	n.r.	0.00468	n.r.	Maeda (1991) Doc. No.: A54655
Cyprinus carpio (mirror carp)	static acute test 96 hours	OECD	>1000	180	Fischer (1990b) Doc. No.: A43501
Lepomis macrochirus (bluegill sunfish)	static acute test 96 hours	EPA	100 - 1000	56	Fischer (1990c) Doc. No.: A43500
Oncorhynchus mykiss (rainbow trout)	static acute test 96 hours	EPA	>1000	56	Fischer (1990d) Doc. No.: A43502

LC_{50} concentration for a 50% mortality of the test population

EC_{50} in Daphnia: concentration for an immobilisation of 50% of the test organisms
in algae: concentration for a 50% inhibition in growth

NOEC no observed effect concentration

n.r. not reported

8.1.1 Green algae

The effect of the technical substance on unicellular planktonic algae was analysed in a growth inhibition test with the green alga *Scenedesmus subspicatus* according to OECD guideline. The following nominal concentrations were tested: control, solvent control (acetone), 100, 180, 320, 560 and 1000 mg/L. After 72 hours test duration the concentration inhibiting the algal growth (comparison of biomass) by 50% , E_bC_{50}, was greater than the highest tested concentration of 1000 mg/L. The concentration of no observed effects, NOEC, was 1000 mg/L (Fischer, 1990a, Doc. No.: A43486).

ACTIVE SUBSTANCE:

POINT 8: **DATA ON THE ECOTOXICOLOGICAL EFFECTS OF THE ACTIVE INGREDIENT**

8.1.2 Acute and chronic toxicity to Daphnia

A test on the acute toxicity of , substance technical, against aquatic invertebrates was carried out with *Daphnia magna* according to OECD guideline. The following concentrations were tested: test A: 10, 5.6, 3.2, 1.8, 1.0, 0.56, 0.32, 0.18, 0.1, 0.056, 0.032, 0.018, 0.01, 0.0056, 0.0032, 0.0018 and 0.001 mg/L; test B: 1.0, 0.56, 0.32, 0.18, 0.10, 0.056, 0.032, 0.018, and 0.01 µg/L. The concentration where 50% of the water flea were immobilised, EC_{50}, was calculated after 24 hours test duration at 0.063 mg/L and after 48 hours test duration at 0.004 mg/L. The concentration of no observed effects, NOEC, was 0.00018 mg/L (Fischer, 1987, Doc. No.: A44380).

A 21 day test on reproduction and growth of *Daphnia magna* was performed with according to US-EPA guideline, which is equivalent to OECD guideline. Nominal test substance concentrations were control, solvent control (acetone), 0.032, 0.056, 0.1, 0.18, and 0.32 µg/L. First juveniles were observed on day 7 in the control and the solvent control, on day 9 in all concentrations except the highest concentration, on day 12 in the concentration of 0.32 µg/L. No significant mortality was observed in any of the concentrations tested. Production of offspring was significantly reduced in all concentrations between days 9 and 14 compared to the control or the solvent control. In the lowest two concentrations of 0.032 and 0.056 µg/L these effects were transient and compensated after 21 days. Significant differences regarding the reproduction rate in comparison with the control groups after 21 days were observed in the concentrations equal to and higher than 0.1 µg/L. Significant differences of carapace length were not concentration related. The concentration without any observed effects on immobilisation, growth of the daphnids, development of embryos, and reproduction was found after 21 days at 0.056 µg/L (Heusel, 1992, Doc. No.: A49194).

8.1.3 Acute toxicity to fish

Tests on the acute toxicity of To fish was carried out with three species: *Cyprinus carpio* (mirror carp), *Lepomis macrochirus* (bluegill sunfish), and *Oncorhynchus mykiss* (former: *Salmo gairdneri*, rainbow trout). All tests were performed far above the water solubility of the compound, which was measured at 0.001 mg/L at 20 °C (Görlitz et al., 1987, Doc. No.: A41447). Observation of intoxication symptoms were severely hindered due to the high turbidity of the test solution.

In the test with mirror carp, no mortality was observed in any of the concentrations tested (control, solvent control (TWEEN 80), 100, 180, 320, 560, and 1000 mg/L). Therefore the LC_{50} was higher than the highest tested

concentration of 1000 mg/L. Intoxication symptoms were swimming at the water surface in concentrations of and higher than 320 mg/L. The NOEC was 180 mg/L (Fischer 1990b; Doc. No.: A43501).

Concentrations in the test with bluegill sunfish were untreated control, solvent control (TWEEN 80), 100, 180, 320, 560, and 1000 mg/L in one test and untreated control, solvent control, 5.6, 10, 18, 32, and 56 mg/L in a second test. Mortality between 20 and 50% was observed in the concentrations from 100 to 1000 mg/L. The LC_{50} thus was between 100 and 1000 mg/L. No mortality was observed in concentrations of and lower than 56 mg/L. Intoxication symptoms in concentrations of 100 mg/L and higher were narcotic conditions. The NOEC thus was 56 mg/L (Fischer 1990c; Doc. No.: A43500).

In the test with rainbow trout, the following concentrations were tested: untreated control, solvent control (TWEEN 80), 100, 180, 320, 560, and 1000 mg/L in one test and untreated control, solvent control, 5.6, 10, 18, 32, and 56 mg/L in a second test. Mortality between 10 and 20% was observed in the concentrations from 100 to 1000 mg/L. No mortality was observed in concentrations of and lower than 56 mg/L. The LC_{50} thus was above the highest tested concentration of 1000 mg/L. No intoxication symptoms could be observed. The NOEC thus was 56 mg/L (Fischer 1990d; Doc. No.: A43502).

8.1.4 Other aquatic organisms

A 96 hour acute toxicity test with the technical substance was carried out using freshwater shrimp (*Palaemon aucidens*) under flow-through condition. 48 hour LC_{50} was 0.02 mg/L and the 96 hour LC_{50} was 0.00468 mg/L. 96-hour minimum concentration causing 100% mortality was 0.02 mg/L. 96 hour maximum concentration causing no mortality was not determined in this test (Maeda, 1991, Doc. No.: A54655).

8.2 Toxicity to terrestrial organisms

substance technical has only negligible effects on soil microflora and is not toxic to earthworms and is of a very low toxicity to birds. It is highly toxic to honey bees.

8.2.1 Soil microflora

Soil respiration:

The possible effect of the technical substance on aerobic soil respiration was observed in loamy sand and clayey silt over a period of 28 days at the dosage of 0.316 kg/ha and the five-fold dosage of 1.58 kg/ha corresponding to soil concentrations of 0.4 and 2.0 mg/kg soil. Respiration rates were determined at

concentration of 1000 mg/L. Intoxication symptoms were swimming at the water surface in concentrations of and higher than 320 mg/L. The NOEC was 180 mg/L (Fischer 1990b; Doc. No.: A43501).

Concentrations in the test with bluegill sunfish were untreated control, solvent control (TWEEN 80), 100, 180, 320, 560, and 1000 mg/L in one test and untreated control, solvent control, 5.6, 10, 18, 32, and 56 mg/L in a second test. Mortality between 20 and 50% was observed in the concentrations from 100 to 1000 mg/L. The LC_{50} thus was between 100 and 1000 mg/L. No mortality was observed in concentrations of and lower than 56 mg/L. Intoxication symptoms in concentrations of 100 mg/L and higher were narcotic conditions. The NOEC thus was 56 mg/L (Fischer 1990c; Doc. No.: A43500).

In the test with rainbow trout, the following concentrations were tested: untreated control, solvent control (TWEEN 80), 100, 180, 320, 560, and 1000 mg/L in one test and untreated control, solvent control, 5.6, 10, 18, 32, and 56 mg/L in a second test. Mortality between 10 and 20% was observed in the concentrations from 100 to 1000 mg/L. No mortality was observed in concentrations of and lower than 56 mg/L. The LC_{50} thus was above the highest tested concentration of 1000 mg/L. No intoxication symptoms could be observed. The NOEC thus was 56 mg/L (Fischer 1990d; Doc. No.: A43502).

8.1.4 Other aquatic organisms

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Soil respiration:

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days 0, 7, 14 and 28 after addition of the test substance during a 12 hour measuring interval after addition of Glucose (4000 mg/kg). Respiration rate in the treatment groups was not significantly different from the control. Therefore the possible impact on soil respiration was rated as negligible even at the highest tested application rate (Baedelt & Frings, 1992, Doc. No.: A48467).

Nitrogen conversion:

The possible effect of the technical substance on nitrogen conversion (nitrification) after addition of ammonium sulfate was tested in loamy sand and silty loam over a period of 28 days at the dosage of 0.316 kg/ha, the five-fold dosage of 1.58 kg/ha, and the ten-fold dosage of 3.16 kg/ha, corresponding to soil concentrations of 0.4, 2.0 and 4 mg/kg soil. Nitrification of ammonium sulfate was determined at 0, 7, 14, 21 and 28 days after addition of the test substance. Nitrogen conversion was rapid and not significantly different from the control even at the highest application rate. Therefore the possible impact on nitrification was rated as negligible even at the highest application rate (Altmannsberger et al. 1988; Doc. No.: A40219).

8.2.2 Soil fauna

The acute effect of the technical substance on earthworms of the species *Eisenia fetida andrei* was examined in an artificial soil test. No mortality occurred in any of the concentrations tested. The LC_{50} thus was higher than the highest tested concentration of 1000 mg/kg soil (dry weight). No intoxication symptoms were detected, weight losses of worms were not statistically different from the control. The NOEC thus lay at 1000 mg/kg (Fischer and Schulze, 1988; Doc. No.: A38801).

8.2.3 Other terrestrial organisms

Results of tests on mammals are summarised separately.

8.2.4 Honey bees

The oral toxicity and contact toxicity of substance technical, to honey bees (*Apis mellifera*) was investigated in the laboratory. Results indicate that technical has a relatively high level of acute toxicity via both contact and oral routes to the honey bee (Bock, 1988, Doc.No.: A39979).

Type of administration	Duration in hours	LD_{50} µg a.i./bee
Oral	24	0.503
	48	0.434
Contact	24	0.020

	48	0.001

8.2.5 Toxicity to birds

Table: Toxicity of , substance technical to birds

Test organism	Test design	LC/LD$_{50}$	NOEL/NOEC	Reference
Colinus virginianus (Bobwhite quail)	acute oral toxicity	>2250 mg/kg b.w.	2250 mg/kg b.w.	Lloyd et al., 1991, Doc. No.: A46539
Coturnix coturnix japonica (Japanese quail)	acute oral toxicity	>2000 mg/kg b.w.	2000 mg/kg b.w.	Ebert and Leist, 1988a, Doc. No.: A38561
Anas platyrhynchus (Mallard duck)	acute oral toxicity	>2000 mg/kg b.w.	2000 mg/kg b.w.	Ebert, 1988a, Doc. No.: A39517
Colinus virginianus (Bobwhite quail)	dietary toxicity	>5620 ppm (approx. 3476 mg/kg body weight/day)	5620 ppm (approx. 3476 mg/kg body weight/day)	Grimes et al., 1991, Doc. No.: A46675
Coturnix coturnix japonica (Japanese quail)	dietary toxicity	>5000 ppm (approx. 1143 mg/kg body weight/day)	2500 ppm (approx. 687 mg/kg body weight/day)	Ebert 1988b, Doc. No.: A39249
Anas platyrhynchus (Mallard duck)	dietary toxicity	>5000 ppm (approx. 1676 mg/kg body weight/day)	5000 ppm (approx. 1676 mg/kg body weight/day)	Ebert and Leist 1988b, Doc. No.: A39251

Acute oral toxicity:

Bobwhite quail (*Colinus virginianus*): In an acute oral LD$_{50}$ study, groups of 5 male and 5 female quails, 17 weeks old, were dosed at 0, 292, 486, 810, 1350 and 2250 mg , substance technical. Doses were administered by gavage into the stomach using corn oil. The observation period was 14 days. There were no treatment related mortalities or overt signs of toxicity at any of the dosage levels tested. A hen at the 810 mg/kg dosage level was noted as ruffled and lethargic from the morning of day 8 until study termination. The hen also showed intermittent signs of reduced reaction to external stimuli during that same period. Gross necroscopy showed an extreme loss of body mass; however, the gastrointestinal tract contained feed. The hen's condition was not considered treatment related. All other birds at all dosages were normal in appearance and behaviour throughout the test period. When compared to the controls, there were

no treatment related effects on body weights or feed consumption. A hen at the 486 mg/kg dosage and the hen that displayed clinical signs at the 810 mg/kg dosage showed declines in body weight at the day 14 body weight interval. These losses were not dose responsive and were considered incidental to treatment. In conclusion, the acute oral LD_{50} value was determined to be greater than 2250 mg/kg body weight. The no mortality level was 2250 mg/kg body weight (Lloyd et al., 1991, Doc. No.: A46539).

Japanese quail (*Coturnix coturnix japonica*): In an acute oral LD_{50} study, groups of 5 male and 5 female Japanese quails, 6 months old, were dosed at 0, 1000 and 2000 mg substance technical/kg body weight. Doses were administered by gavage into the stomach using sesame oil. The observation period was 2 weeks. No mortality and no clinical signs of intoxication was observed in any of the dosages tested. Food consumption was lower in the highest dosage until the third day after application without impact on body weight.

The LD_{50} value was higher than 2000 mg / kg body weight. The no observed effect level was established at 2000 mg/ kg body weight (Ebert and Leist, 1988a, Doc. No.: A38561).

Mallard duck (*Anas platyrhynchus*): In an acute oral LD_{50} study, groups of 5 male and 5 female Mallard ducks, 6 months old, were dosed at 0, 1000 and 2000 mg substance technical/kg body weight. The doses were administered in sesame oil into the stomach. The observation period was 14 days. No mortality and no clinical signs of intoxication were observed in any of the dosages tested. Food consumption and body weight was not influenced by the test substance. **The LD_{50} value was higher than 2000 mg/kg body weight** (Ebert, 1988a, Doc. No.: A39517).

Short-term toxicity:

Bobwhite quail : Five groups each consisting of 10 quail chicks, 10 days old at the start of treatment, received , substance technical, in the daily diet in concentrations of 562, 1000, 1780, 3160 and 5620 ppm over a period of 5 days. After this time the chicks received diet without test substance for a further 3 days. Each of the studies included 5 control groups. There were no treatment related mortalities or overt signs of toxicity at any of the concentrations tested. One bird at the 3160 ppm concentration was found dead on the afternoon of day 3. Based on necroscopy results, the mortality was not considered treatment related. All other birds were normal in appearance and behaviour throughout the study. When compared to the control, there was no effect on body weights or feed consumption at any concentration. In conclusion, the dietary LC_{50} value was

determined to be greater than 5620 ppm, equivalent to a mean daily substance intake of approx. 3476 mg/kg body weight. The no mortality level was 5620 ppm. The no observed effect concentration was 5620 ppm (Grimes et al., 1991, Doc. No.: A46675).

Japanese quail: Six groups each consisting of 10 chicks , 11 days old at the start of treatment, received , substance technical in the daily diet in concentrations of 0, 312.5, 625, 1250, 2500 and 5000 mg / kg diet (ppm) over a period of 5 days. After this time the chicks received diet without test substance for a further 3 days. One animal in the 5000 ppm group died during the night between days 4 and 5 of the study without clinical signs having been observed. In all other test groups no mortality occurred. No clinical signs of intoxication could be observed at any treatment group. Food consumption and body weight gains remained unaffected by the test substance in all treatment groups. Thus, **the LC_{50} is with certainty greater than 5000 ppm, equivalent to a mean daily substance intake of approx. 1145 mg/kg body weight.** The no observed effect level was considered to be 2500 ppm, equivalent to approximately 687 mg/kg body weight. (Ebert 1988b, Doc. No.: A39249).

Mallard duck : Six groups each consisting of 10 ducklings, 11 days old at the start of treatment, received , substance technical in the daily diet in concentrations of 0, 312.5, 625, 1250, 2500 and 5000 mg / kg diet (ppm) over a period of 5 days. After this time the chicks received diet without test substance for a further 3 days. No mortality occurred in any of the treated groups. No clinical signs of intoxication occurred in any of the dose groups at any time during the study. Food consumption and body weight gains remained unaffected by the test substance in all treatment groups. Thus, the LC_{50} is with certainty greater than 5000 ppm, equivalent to a mean daily substance intake of approx. 1676 mg/kg body weight. The no observed effect level was considered to be 5000 ppm (Ebert and Leist, 1988b, Doc. No.: A39251).

Evaluation

Classification and labelling

Substance technical must be classified as follows:

"very toxic to aquatic organisms" (R50)

"may cause long-term adverse effects in the aquatic environment" (R53)

"dangerous for the environment" (hazard symbol N)

ACTIVE SUBSTANCE:

POINT 8: DATA ON THE ECOTOXICOLOGICAL EFFECTS OF THE ACTIVE INGREDIENT

Justification for the labelling is as follows:

- high toxicity to aquatic invertebrates (EC_{50} < 1 mg/L),
- bioaccumulation potential (bioconcentration factor in fish > 100)
- lack of ready degradability

Release to the environment (soil, water) should be avoided (S61).

Furthermore . is not toxic to birds, earthworms and soil microflora but toxic to honey bees.

ACTIVE SUBSTANCE:

POINT 9: INFORMATION ON OBSERVED EFFECTS OF THE ACTIVE INGREDIENT OR PRODUCT

9 INFORMATION ON OBSERVED EFFECTS OF THE ACTIVE INGREDIENT OR PRODUCT

9.1 Incidents of exposure to the active ingredient and product

9.1.1 Humans

9.1.1.1 Investigations

No studies have been carried out on humans to date.

9.1.1.2 Observations within the company

No incidents of inadvertent exposure to have been reported to date.

9.1.2 Livestock, pets and other animals

No incidents of inadvertent exposure to have been reported to date.

9.1.3 Ornamental, agricultural and other plants

No phytotoxic properties of to agricultural crops have been observed during the development of this compound.

9.2 Practical experience on the contamination of soil water or air by:

9.2.1 Use of the product and storage of treated wood

No incidents have been reported concerning the application to treated wood, the storage of treated wood or the disposal of treated wood since the compounds first commercial use in Japan in 1992.

9.2.2 Use of treated wood

see 9.2.1

9.2.3 Disposal of treated wood and unused product

see 9.2.1

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

10 CONCLUDING EXPERT EVALUATION ON USE OF THE PRODUCT

10.1 Risks for human health

Refer to expert evaluation on product submitted by Weyl GmbH

10.2 Risks for the environment

Refer to expert evaluation on product submitted by Weyl GmbH

11 REFERENCES

Point 3:

A38037 Plant Protection / Substance Identity
Kehne
Hoechst Pfl.Fo.Chem., DEU
Ber.-Nr.: Ke288
08.04.1988

A43077 substance, pure. Density
Roechling; Rexer, K.
Hoechst C Forsch.Formulierung, DEU
Ber.-Nr.: WIR0094(06)
19.04.1990

A40002 Determination of vapour pressure as a function of temperature of
Grewer
Hoechst Angew.Phys., DEU
Ber.-Nr.: S87/1168
28.01.1988

A41447 - Solubility in water
Goerlitz, G.; Eyrich, U.; Dorn, E.
Hoechst C Produktentwicklung Oekologie 1, DEU
Ber.-Nr.: CP87/058
02.08.1989

A40028 , solubility in organic solvents
Goerlitz, G.; Eyrich, U.
Hoechst Analyt.Labor., DEU
Ber.-Nr.: CP056/88
24.11.1988

A43166 , determination of the partition coefficient n-octanol/water (log P) using HPLC
R 19900323
Weilbaecher, R.; Goerlitz, G.

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

Hoechst C Produktentwicklung Oekologie 1, DEU
23.93.1990

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

A49606 technical. Purity
Kehne
Hoechst C Forsch.Chemie, DEU
Ber.-Nr.: KE882
02.02.1993

A49801 Plant Protection / Substance Identity
Kehne
Hoechst C Forsch.Chemie, DEU
Ber.-Nr.: KE884
22.02.1993

A49802 Plant Protection / Substance Identity
Kehne
Hoechst C Forsch.Chemie, DEU
Ber.-Nr.: KE885
22.02.1993

A49607 technical. Impurities
Kehne
Hoechst C Forsch.Chemie, DEU
Ber.-Nr.: KE881
02.02.1993

A45954 , Determination of the Dissociation Constant K(Diss)
Schollmeier, M.
Hoechst C Produktentwicklung Oekologie 1, DEU
Ber.-Nr.: OE91/065
20.06.1991

A50651

Determination of the abiotic hydrolysis as a function of pH according to EPA Pesticide Assessment Guideline, Subdivision N, 161-1

Schollmeier, M.; Eyrich, U.
Hoechst C Produktentwicklung Oekologie 1, DEU
Ber.-Nr.: CP055/88

A44205

5.1.10 Special toxicity studies

Acute delayed neurotoxicity in adult hens

(96.8 %), as original, was administered twice orally at the limit dose of 5000 mg/kg body weight to 12 White Leghorn hens, with an interval of 21 days between each application. A negative control (sesame oil, 4.6 ml/kg body weight) and a positive control (TOCP, 500 mg/kg body weight), each composed of 6 hens, were also included in the study. The neurotoxicity study was preceded by an acute oral toxicity study of the test substance (LD_{50}).

After treatment with the test substance no clinical signs of intoxication were observed and all hens survived until the end of the study. No clinical signs of delayed neurotoxicity in the form of ataxia could be established. Histopathological examination of brain, spinal cord and peripheral nerves indicated no pathomorphological lesions. In contrast, the hens in the positive control group (TOCP) showed the typical neurotoxic effects produced by this reference substance in the form of prolonged delayed-onset severe ataxia or, in some of the animals, paralysis, together with pathomorphological lesions especially in the form of damage to myelinised nerve fibres. These lesions were strongly marked in the substantia alba of all segments of the spinal cord, and less pronounced in the tractus spinocerebellaris of the medulla oblongata; microscopic examination showed them to be axonal swellings. Based on these results was considered to cause no Organophosporus Induced Delayed Neurotoxicity (OPIDN) at the maximum recommended dose level of 5000 mg/kg body weight.

A45316

5.1.11 Publications about toxicology of the active ingredient

Data not available.

ACTIVE SUBSTANCE:

POINT 5: INFORMATION ON TOXICOLOGY

5.2 **Acute toxicity of the formulated product**

Please refer to the file on the Products submitted by the Weyl Company.

5.2.1 **Rat oral**

See above

5.2.2 **Rat dermal**

See above

5.2.3 **Rat inhalation**

See above

5.2.4 **Rabbit skin irritation**

See above

5.2.5 **Rabbit eye irritation**

See above

ACTIVE SUBSTANCE:

POINT 6: INFORMATION ON RELEASE OF THE ACTIVE INGREDIENT INTO THE ENVIRONMENT

6 INFORMATION ON RELEASE OF THE ACTIVE INGREDIENT INTO THE ENVIRONMENT

The release of the active substance into the environment on the properties of the active substance in the formulation (water soluble concentrate) and also dependent on the envisaged use pattern. The application areas of the product to be considered will cover risk classification 1 to 3 (according to DIN 68800). Application restrictions will be imposed for

- wood which may come into direct contact with food or animal feeding stuffs

- >extensive building components of wood [surface to volume ratio equal to or greater than 0.2 (m^2/m^3)] inside or as delimitation of rooms intended as permanent quarters for humans or animals or as storage areas for food or animal feeding stuffs.

The only permitted application technique will be vacuum pressure impregnation (VPI). Brushing, spraying (mistblowing), dipping and tank immersion will not be permitted.

To prevent leaching immediately after the impregnation process the wood must be protected against rain for a minimum time of 24 h.

6.1 Release in the air

To investigate the release of the active substance into the air (evaporation rate/air concentration) a model study was performed (EMPA, 1994, Doc. No.: A53081) using a microchamber with an internal volume of 1790 cm^3. A 20 cm^2 area on the surface of a wood sample (type of wood: deal, sapwood) was treated, resulting in a surface to volume ratio of ≈ 1.1 (m^2/m^3). The air flow (synthetic air, 20°C, 44% relative humidity) was adjusted to give an air turnover rate of 1 h^{-1}. The emission of was investigated over a period of 29 days.

The study was conducted following a design in agreement with BGVV (Dr. Westphal).

was applied at a rate of 568 mg per m^2. The active substance was applied as 0.15 % LOSP formulation „Defence Anti Insect Sila" (Ref. No. 93042)

After the application (duration: 85 min) the wooden block was dried at 25°C and 35% rH for 90 min. Sampling was performed by adsorption on Tenax adsorption tubes consisting of a n adsorbing and retarding layer. Sampling intervals in the first week were alternatively 2 and 20 h respectively, starting with a two-hour interval immediately after the wood had been placed in the microchamber (start of emission subsequently. On days 14 to 12, 21 to 22 and 28 to 29, sampling was

done in 20 h intervals. Furthermore a long-term sampling was performed from day 8 to day 14 over a 146 h interval.

ACTIVE SUBSTANCE:

POINT 6: INFORMATION ON RELEASE OF THE ACTIVE INGREDIENT INTO THE ENVIRONMENT

Table 1: Results of EMPA trial

[application of 568 mg spruce wood; air turnover rate 1 h^{-1}; surface to volume ratio ≈ 1.1 (m^2/m^3); carrier gas synthetic air, 20°C, 44% rH]

days after application	sampling interval [h]	concentration in carrier gas [ng m^{-3}]	emission from wood [ng m^{-2} h^{-1}]
0	2	106	95
0-1	20	3.9	3.5
1-2	20	0.8	0.8
8 - 14	146	1.1	1.0
27-28	21	2.6	2.4

6.1.1 Maximum diffusion rate

A maximum evaporation rate of 95 ng m^{-2} h^{-1} could be calculated from the measured air concentration of the active substance during the first two hours. It should be noted in this connection, however, that there is a possibility with the first sampling interval, that very small amounts of wood-dust containing active substance may be transported by the carrier gas from the emission source to the adsorption tube. This is probably the reason why a rather high substance release via the gas phase was recorded, especially for the first sampling interval. During this period small particles of treated wood dust may have been transported by the transport gas from the source of emission to the adsorption tube.

A realistic estimate of the evaporation rate can be deduced from the measurements from day 1 to day 28 with evaporation rates between 0.8 and 3.5 ng m^{-2} h^{-1}.

6.1.2 Concentration expected indoors in the air of a room

The measured air concentrations within these trials can be taken as a direct estimate of an indoor air concentration under worst case conditions (surface to volume ratio of ≈ 1.1 m^2/m^3, air turnover rate of 1 h^{-1}, air temperature 20°C, relative humidity 44%).

A maximum concentration of of 106 ng m^{-3} was measured at the very beginning of the trial (first two hours). This value is of no relevance in view of the envisaged use pattern: in the case of the vacuum pressure impregnation the treated wood is kept at the manufacturer for at least 24 h for leaching protection (cf. 6).

The estimated rate of evaporation from treated wood surfaces should therefore be more orientated to the values for "aged "samples of day 1 to 28. Thus an indoor concentration of about 2 ng m^{-3} (span between 0.8 and 3.9 ng m^{-3}) over a 28 day time period can be expected.

These experimental values are well below the saturation concentration for in air (420 ng/m^3), an approximate value obtained on the basis of the vapour pressure of (Grewer, 1988, Doc. No.: A40002.)

6.1.3 Evaporation of the active ingredient caused by the solvent

The evaporation trials were conducted with a 0.15 % LOSP formulation (cf. 6.1.1).

6.2 Release into soil or water

No study was presented from which a direct leaching rate can be derived.

Indirect hints possibly can be concluded from efficacy trials with an accelerated ageing of the wood according to EN 84 (leaching procedure), where the efficacy of the test formulation results gave no evidence for any leaching of the active substance from treated wood samples. Active substance contents in the leachates were not analysed (ÖHFI, 1993)

A direct release into the soil compartment is not relevant because no application according to risk classification 4 of (wood with steady soil contact) is intended.

6.2.1 Maximum leaching rate

See above.

6.2.1.1 in fresh water

See above.

6.2.1.2 in ocean water

See above.

6.3 Reactions that can change the rate of release

No reactions known.

7 BEHAVIOR OF THE ACTIVE INGREDIENT IN THE ENVIRONMENT

7.1 Behavior in soil

7.1.1 Degradation and metabolism in soil

Aerobic soil metabolism:

The fate of the active substance was investigated in four soils (sandy loam, sand, loamy sand and a silt loam) under aerobic conditions at a temperature of 20 ± 2°C. The substance was applied onto the soil at a rate of 300 g/ha (0.4 mg/kg soil) and incubated up to 128 days.

Sampling of two replicates of each soil was done on days 4 (6), 8 (9), 16, (31) 32, (48) 49, 64, 80 and 128 (values in brackets are times for the loamy sand samples). The material balance for the end of the experiment (day 128) is summarized in **Table I.**

Table I: Material balance for degradation of in four soils at the end of the experiment (day 128 after application)

Soil	Volatiles ** [%]*	Extractables [%]*	Non-extractable Residues [%]*	Recovery** * [%]*
Sandy loam	10.4	29.3	43.1	82.7
Sand	3.3	37.0	41.7	82.2
Loamy sand	9.4	56.0	22.4	87.9
Silt loam	13.7	31.3	40.1	85.1

* all values given in % of total applied radioactivity, mean value of two replicates

** other volatiles than $^{14}CO_2$ were detected to < 0.4 %

*** poor recoveries may result from adsorption of to glass surfaces due to high log P_{ow}

Between 29 % (sandy loam) and 56 % (loamy sand) of total applied radioactivity were still extractable on day 128. Slow mineralisation was detected for the sand (3 %) increasing to moderate rates (14 %) for the silt loam. The main portion of extractable radioactivity consisted of unchanged parent compound (81 to 100 %). At least three metabolites were observed in a total of < 17 % (< 0.07 mg/kg)

during the incubation period. Identification was not feasible due to the low concentration and their inconsistent appearance in the course of the study. Consequently, a degradation scheme cannot be presented. On the other hand, degradation products showed no tendency for an accumulation in soil. The initial step of breakdown sequence must therefore be assumed as the slowest which is then followed by a rapid degradation of the metabolites.

DT_{50} and DT_{90} values[1] were calculated assuming a first order kinetics and are shown in **Table II** for the individual soils.

Table II: Half-lives of in soils under aerobic conditions

Soil	DT_{50} [days]	DT_{90} [days]
Sandy loam	72	237
Sand	91	303
Loamy sand	148	490
Silt loam	85	281

It was therefore demonstrated that is finally mineralised under aerobic conditions (Schwab, 1992, Doc. No.: A49193).

Anaerobic degradation:

Phenoxy-UL-^{14}C-labelled was applied to a sandy loam soil at an application rate of 300 g/ha (0.4 mg/kg soil) and at 20 ± 2°C. After an aerobic starting and ageing phase for 30 days, conditions were converted to anaerobics by flooding the samples with water and purging the atmosphere above the samples with nitrogen. After establishment of anaerobic conditions (day 48, 18 days after flooding), further samples were collected on days 78, 108 and 143 after application (e.g. day 0, 30, 60 and 95 of anaerobic phase).

During the incubation period, extractability from soil remained nearly constant with a slow decrease from 95.8 % (day of application) to 76.4 - 83.0 % at the end of the study (day 143). Consequently, slow formation of $^{14}CO_2$ was observed accounting for 3.1 % on day 143. Other volatile degradation products were detected to < 0.1 % of total applied radioactivity. Non-extractable residues

[1] DT_{50}: disappearance time of 50 % extractable parent compound
DT_{90}: disappearance time of 90 % extractable parent compound

increased from 0.4 % (day 0) to 7.5 - 13.3 % on day 143. No noticeable metabolite was detected, therefore the active substance was the relevant extractable residue.

A half-life time for dissipation of the anaerobic phase cannot be given, as no decrease of the concentration of in soil was observed under anaerobic conditions.

On the other hand, very low amounts of radioactivity were desorbed from soil particles. 0.5 - 3.5 % of total applied radiolabel were measured in the water phase after flooding (Schwab, 1992, Doc. No.: A49300).

The marginal desorption of from soil particles will thus not lead to high concentrations of the test substance in water even after a heavy rainfall event when assuming a runoff of soil into an aquatic ecosystem.

Aerobic aquatic metabolism:

The degradation of was studied under aerobic conditions in two sediment/water systems (a silt loam, "Nidda", and a sand, "Schwanheim") at 20 ± 2°C. Application was done on the basis of 0.124 kg a.s.[2]/ha water surface with sampling intervals on days 0, 3, 7, 14, 30, 92, 120, 182 and 241.

0.4 % (silt loam sediment) and 3 % (sand) of radiolabel applied were still present in the water phase on day 241 after application. At the same time, extractability from the sediments decreased constantly to approx. 19 - 24 % for the silt loam and 8 to 16 % for the sand sediment. Non-extractable residues were detected to 36 % (silt loam) and 47 - 54 % for the sand. 24 - 26 % of the radiolabel were found mineralised in the silt loam, 22 - 24 % in the sand system.

Other degradation products (nine in total) were observed in small percentages (each < 7 % of total applied radioactivity) during the incubation period.

By assuming a first order kinetics, the following half-lives were calculated which are presented in **Table III**.

Table III: DT_{50} and DT_{90} values for dissipation of in two sediment/water systems

Water / sediment system	DT_{50} [days] water	DT_{90} [days] water	DT_{50} [days] sediment	DT_{90} [days] sediment	DT_{50} [days] water/sediment	DT_{90} [days] water/sediment
Silt loam ("Nidda")	14.4*	47.7*	120.7	401.0	110.7	367.8

[2] a.s.: active substance

Sand ("Schwanheim")	1.4	4.5	100.1	332.6	84.4	280.4

*as a result of a check of data in the original report, adsorption of to the sediment is at least as fast as for the sand. Due to an error in calculation of dissipation times, higher values were reported. An amendment to this report is in preparation.

is rapidly eliminated from the water phase to the sediment, where the compound is finally mineralised. As no degradation products accumulated in the course of the study, the first step in degradation can be again assumed as the slowest process (Schwab, 1992, Doc. No. A49239).

As the dissipation of from the water phase is fast, no long term exposure of aquatic organisms to the parent compound is likely to occur (for more details see also chapter 8).

7.1.2 Adsorption / Desorption

(according to OECD Guideline 106). In addition, data on leaching, if available

A detailed study on the adsorption / desorption behaviour to soils was not carried out. From the high octanol/water coefficient (chapter 3.8), it must be concluded that a strong adsorption of the compound to organic matter of soil can be expected. An estimation of the K_{OC} value based on the octanol/water partition coefficient was made by Görlitz (1991, Doc. No.: A46678) and resulted in a K_{OC} of 10^5. Thus the compound has no leaching potential which is also underlined by a leaching study summarized below.

Column leaching:

The leaching potential of non-aged and aged (90 days) , formulated as , was investigated in three german standard soils 2.1, 2.2 and 2.3 (corresponding to a sand, loamy sand and sandy loam). Following an application rate of 300 g/ha and an (extreme) irrigation rate corresponding to 200 mm rain over 48 hours, between 0.41 and 1.14 % of radiolabel were detected in the leachates for non-aged samples. For aged samples, an average of 0.75 % (maximum value: 0.86 %) was determined under the same conditions. Neither nor its degradation products thus show a mobility and they must be considered as immobile in soil (Buettner, 1990, Doc. No. A44748).

is not intended for use on wood/timber which is in a steady contact to water. Due to a general tight binding of the compound to organic matter (lignine/cellulose particles of wood), leaching from treated wood is unlikely to occur, especially if the wood is moistened only occasionally in a rainfall event.

For this case, only a very minor release of active substance to compartments of the environment (water and/or soil) is likely to occur.

7.2 Behavior in water

Not relevant, as the formulated material will not be used for timber in a steady contact with water.

7.2.1 Degradation and metabolism

See above

7.2.2 Adsorption / desorption in sediment

See above

7.3 Bioaccumulation

The bioconcentration and successive depuration of

in fish was conducted with bluegill sunfish (Lepomis macrochirus) in a dynamic study for a total of 70 days.

During an uptake period of 28 days, a flow-through system maintained an average concentration of 1.85 µg a.s./L water. This was followed by a 42 day depuration phase in clean water.

Bioconcentration factors (BCF) were determined for the whole fish as well as for edible and non-edible parts on days 0, 1, 3, 7, 14, 21 and 28 of the uptake phase. Five fish were sacrificed at each date, three were separated into edible/non-edible parts and two were taken as a whole for the analysis as a complete fish. During the depuration period, sampling was made on days 1, 3, 7, 10, 14, 17, 21, 28, 35 and 42. With the exception on days 17, 21, 28 and 35 (only two fish), three fish were investigated at each timepoint for edibles/non-edibles. Whole fish samples were analysed in duplicate until day 14 and, up to the end of the study, one fish was sampled during the depuration. For investigation of metabolism, 15 further fish were collected during the uptake on days 3 and 21.

A plateau concentration of radioactivity was reached between day 20 and 28. On day 28, concentration in the tissue of edible parts (fillet body, muscle, skin and skeleton) had increased to 0.769 mg a.s. equiv./kg fish. For non-edible parts (head, fins, viscera), 3.235 mg a.s. equiv./kg fish were determined. Finally, for the whole fish a concentration of 1.601 mg a.s. equiv./kg fish was found. Daily bioconcentration factors were determined to 411 for edibles and 1728 for non-edible parts on day 28, whereas for the whole fish a factor of 905 was calculated on day 21.

Elimination of the compound takes place on a moderate level with half-life times of 30 to 40 days.

Besides three minor degradation products (total: 9 % of radiolabel applied) was identified as the only relevant radioactive residue in non-edible tissues. For edible parts, unchanged parent compound was found as the only component.

The low water solubility (1 µg/L) and the high octanol/water partition coefficient (log P_{ow} 8.2) may have suggested an even higher bioconcentration factor (BCF). However, slow accumulation of in fish was observed reaching its highest BCF value of 1728 for non-edible parts only, whereas for the whole test organism a BCF of 905 was determined (Buettner and Fischer, 1988, Doc. No.: A40437).

8 DATA ON THE ECOTOXICOLOGICAL EFFECTS OF THE ACTIVE INGREDIENT

8.1 Toxicity for aquatic organisms

, substance technical, is not acute toxic to fish and green alga, even far above the water solubility, but is highly toxic to aquatic invertebrates.

The following results were obtained with the technical substance:

Test organism	Test design	Test method	LC/EC_{50} (mg/L)	NOEC (mg/L)	Reference
Scenedesmus subspicatus (green alga)	growth inhibition test 72 hours	OECD	>1000	1000	Fischer (1990a) Doc. No.: A43486)
Daphnia magna (water flea)	static acute test 48 hours	OECD	0.004	0.00018	Fischer (1987) Doc. No.: A44380
Daphnia magna (water flea)	reproduction test 21 days	OECD	n.r.	0.000056	Heusel (1992) Doc. No.: A49194
Palaemon aucidens (freshwater shrimp)	flow-through 96 hours	n.r.	0.00468	n.r.	Maeda (1991) Doc. No.: A54655
Cyprinus carpio (mirror carp)	static acute test 96 hours	OECD	>1000	180	Fischer (1990b) Doc. No.: A43501
Lepomis macrochirus (bluegill sunfish)	static acute test 96 hours	EPA	100 - 1000	56	Fischer (1990c) Doc. No.: A43500
Oncorhynchus mykiss (rainbow trout)	static acute test 96 hours	EPA	>1000	56	Fischer (1990d) Doc. No.: A43502

LC_{50} concentration for a 50% mortality of the test population

EC_{50} in Daphnia: concentration for an immobilisation of 50% of the test organisms
in algae: concentration for a 50% inhibition in growth

NOEC no observed effect concentration

n.r. not reported

8.1.1 Green algae

The effect of the technical substance on unicellular planktonic algae was analysed in a growth inhibition test with the green alga *Scenedesmus subspicatus* according to OECD guideline. The following nominal concentrations were tested: control, solvent control (acetone), 100, 180, 320, 560 and 1000 mg/L. After 72 hours test duration the concentration inhibiting the algal growth (comparison of biomass) by 50% , E_bC_{50}, was greater than the highest tested concentration of 1000 mg/L. The concentration of no observed effects, NOEC, was 1000 mg/L (Fischer, 1990a, Doc. No.: A43486).

ACTIVE SUBSTANCE:

POINT 8: **DATA ON THE ECOTOXICOLOGICAL EFFECTS OF THE ACTIVE INGREDIENT**

8.1.2 Acute and chronic toxicity to Daphnia

A test on the acute toxicity of , substance technical, against aquatic invertebrates was carried out with *Daphnia magna* according to OECD guideline. The following concentrations were tested: test A: 10, 5.6, 3.2, 1.8, 1.0, 0.56, 0.32, 0.18, 0.1, 0.056, 0.032, 0.018, 0.01, 0.0056, 0.0032, 0.0018 and 0.001 mg/L; test B: 1.0, 0.56, 0.32, 0.18, 0.10, 0.056, 0.032, 0.018, and 0.01 µg/L. The concentration where 50% of the water flea were immobilised, EC_{50}, was calculated after 24 hours test duration at 0.063 mg/L and after 48 hours test duration at 0.004 mg/L. The concentration of no observed effects, NOEC, was 0.00018 mg/L (Fischer, 1987, Doc. No.: A44380).

A 21 day test on reproduction and growth of *Daphnia magna* was performed with according to US-EPA guideline, which is equivalent to OECD guideline. Nominal test substance concentrations were control, solvent control (acetone), 0.032, 0.056, 0.1, 0.18, and 0.32 µg/L. First juveniles were observed on day 7 in the control and the solvent control, on day 9 in all concentrations except the highest concentration, on day 12 in the concentration of 0.32 µg/L. No significant mortality was observed in any of the concentrations tested. Production of offspring was significantly reduced in all concentrations between days 9 and 14 compared to the control or the solvent control. In the lowest two concentrations of 0.032 and 0.056 µg/L these effects were transient and compensated after 21 days. Significant differences regarding the reproduction rate in comparison with the control groups after 21 days were observed in the concentrations equal to and higher than 0.1 µg/L. Significant differences of carapace length were not concentration related. The concentration without any observed effects on immobilisation, growth of the daphnids, development of embryos, and reproduction was found after 21 days at 0.056 µg/L (Heusel, 1992, Doc. No.: A49194).

8.1.3 Acute toxicity to fish

Tests on the acute toxicity of To fish was carried out with three species: *Cyprinus carpio* (mirror carp), *Lepomis macrochirus* (bluegill sunfish), and *Oncorhynchus mykiss* (former: *Salmo gairdneri*, rainbow trout). All tests were performed far above the water solubility of the compound, which was measured at 0.001 mg/L at 20 °C (Görlitz et al., 1987, Doc. No.: A41447). Observation of intoxication symptoms were severely hindered due to the high turbidity of the test solution.

In the test with mirror carp, no mortality was observed in any of the concentrations tested (control, solvent control (TWEEN 80), 100, 180, 320, 560, and 1000 mg/L). Therefore the LC_{50} was higher than the highest tested

concentration of 1000 mg/L. Intoxication symptoms were swimming at the water surface in concentrations of and higher than 320 mg/L. The NOEC was 180 mg/L (Fischer 1990b; Doc. No.: A43501).

Concentrations in the test with bluegill sunfish were untreated control, solvent control (TWEEN 80), 100, 180, 320, 560, and 1000 mg/L in one test and untreated control, solvent control, 5.6, 10, 18, 32, and 56 mg/L in a second test. Mortality between 20 and 50% was observed in the concentrations from 100 to 1000 mg/L. The LC_{50} thus was between 100 and 1000 mg/L. No mortality was observed in concentrations of and lower than 56 mg/L. Intoxication symptoms in concentrations of 100 mg/L and higher were narcotic conditions. The NOEC thus was 56 mg/L (Fischer 1990c; Doc. No.: A43500).

In the test with rainbow trout, the following concentrations were tested: untreated control, solvent control (TWEEN 80), 100, 180, 320, 560, and 1000 mg/L in one test and untreated control, solvent control, 5.6, 10, 18, 32, and 56 mg/L in a second test. Mortality between 10 and 20% was observed in the concentrations from 100 to 1000 mg/L. No mortality was observed in concentrations of and lower than 56 mg/L. The LC_{50} thus was above the highest tested concentration of 1000 mg/L. No intoxication symptoms could be observed. The NOEC thus was 56 mg/L (Fischer 1990d; Doc. No.: A43502).

8.1.4 Other aquatic organisms

A 96 hour acute toxicity test with the technical substance was carried out using freshwater shrimp (*Palaemon aucidens*) under flow-through condition. 48 hour LC_{50} was 0.02 mg/L and the 96 hour LC_{50} was 0.00468 mg/L. 96-hour minimum concentration causing 100% mortality was 0.02 mg/L. 96 hour maximum concentration causing no mortality was not determined in this test (Maeda, 1991, Doc. No.: A54655).

8.2 Toxicity to terrestrial organisms

substance technical has only negligible effects on soil microflora and is not toxic to earthworms and is of a very low toxicity to birds. It is highly toxic to honey bees.

8.2.1 Soil microflora

Soil respiration:

The possible effect of the technical substance on aerobic soil respiration was observed in loamy sand and clayey silt over a period of 28 days at the dosage of 0.316 kg/ha and the five-fold dosage of 1.58 kg/ha corresponding to soil concentrations of 0.4 and 2.0 mg/kg soil. Respiration rates were determined at

concentration of 1000 mg/L. Intoxication symptoms were swimming at the water surface in concentrations of and higher than 320 mg/L. The NOEC was 180 mg/L (Fischer 1990b; Doc. No.: A43501).

Concentrations in the test with bluegill sunfish were untreated control, solvent control (TWEEN 80), 100, 180, 320, 560, and 1000 mg/L in one test and untreated control, solvent control, 5.6, 10, 18, 32, and 56 mg/L in a second test. Mortality between 20 and 50% was observed in the concentrations from 100 to 1000 mg/L. The LC_{50} thus was between 100 and 1000 mg/L. No mortality was observed in concentrations of and lower than 56 mg/L. Intoxication symptoms in concentrations of 100 mg/L and higher were narcotic conditions. The NOEC thus was 56 mg/L (Fischer 1990c; Doc. No.: A43500).

In the test with rainbow trout, the following concentrations were tested: untreated control, solvent control (TWEEN 80), 100, 180, 320, 560, and 1000 mg/L in one test and untreated control, solvent control, 5.6, 10, 18, 32, and 56 mg/L in a second test. Mortality between 10 and 20% was observed in the concentrations from 100 to 1000 mg/L. No mortality was observed in concentrations of and lower than 56 mg/L. The LC_{50} thus was above the highest tested concentration of 1000 mg/L. No intoxication symptoms could be observed. The NOEC thus was 56 mg/L (Fischer 1990d; Doc. No.: A43502).

8.1.4 Other aquatic organisms

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8.2.1 Soil microflora

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days 0, 7, 14 and 28 after addition of the test substance during a 12 hour measuring interval after addition of Glucose (4000 mg/kg). Respiration rate in the treatment groups was not significantly different from the control. Therefore the possible impact on soil respiration was rated as negligible even at the highest tested application rate (Baedelt & Frings, 1992, Doc. No.: A48467).

Nitrogen conversion:

The possible effect of the technical substance on nitrogen conversion (nitrification) after addition of ammonium sulfate was tested in loamy sand and silty loam over a period of 28 days at the dosage of 0.316 kg/ha, the five-fold dosage of 1.58 kg/ha, and the ten-fold dosage of 3.16 kg/ha, corresponding to soil concentrations of 0.4, 2.0 and 4 mg/kg soil. Nitrification of ammonium sulfate was determined at 0, 7, 14, 21 and 28 days after addition of the test substance. Nitrogen conversion was rapid and not significantly different from the control even at the highest application rate. Therefore the possible impact on nitrification was rated as negligible even at the highest application rate (Altmannsberger et al. 1988; Doc. No.: A40219).

8.2.2 Soil fauna

The acute effect of the technical substance on earthworms of the species *Eisenia fetida andrei* was examined in an artificial soil test. No mortality occurred in any of the concentrations tested. The LC_{50} thus was higher than the highest tested concentration of 1000 mg/kg soil (dry weight). No intoxication symptoms were detected, weight losses of worms were not statistically different from the control. The NOEC thus lay at 1000 mg/kg (Fischer and Schulze, 1988; Doc. No.: A38801).

8.2.3 Other terrestrial organisms

Results of tests on mammals are summarised separately.

8.2.4 Honey bees

The oral toxicity and contact toxicity of substance technical, to honey bees (*Apis mellifera*) was investigated in the laboratory. Results indicate that technical has a relatively high level of acute toxicity via both contact and oral routes to the honey bee (Bock, 1988, Doc.No.: A39979).

Type of administration	Duration in hours	LD_{50} µg a.i./bee
Oral	24	0.503
	48	0.434
Contact	24	0.020

	48	0.001

8.2.5 Toxicity to birds

Table: Toxicity of , substance technical to birds

Test organism	Test design	LC/LD_{50}	NOEL/NOEC	Reference
Colinus virginianus (Bobwhite quail)	acute oral toxicity	>2250 mg/kg b.w.	2250 mg/kg b.w.	Lloyd et al., 1991, Doc. No.: A46539
Coturnix coturnix japonica (Japanese quail)	acute oral toxicity	>2000 mg/kg b.w.	2000 mg/kg b.w.	Ebert and Leist, 1988a, Doc. No.: A38561
Anas platyrhynchus (Mallard duck)	acute oral toxicity	>2000 mg/kg b.w.	2000 mg/kg b.w.	Ebert, 1988a, Doc. No.: A39517
Colinus virginianus (Bobwhite quail)	dietary toxicity	>5620 ppm (approx. 3476 mg/kg body weight/day)	5620 ppm (approx. 3476 mg/kg body weight/day)	Grimes et al., 1991, Doc. No.: A46675
Coturnix coturnix japonica (Japanese quail)	dietary toxicity	>5000 ppm (approx. 1145 mg/kg body weight/day)	2500 ppm (approx. 687 mg/kg body weight/day)	Ebert 1988b, Doc. No.: A39249
Anas platyrhynchus (Mallard duck)	dietary toxicity	>5000 ppm (approx. 1676 mg/kg body weight/day)	5000 ppm (approx. 1676 mg/kg body weight/day)	Ebert and Leist 1988b, Doc. No.: A39251

Acute oral toxicity:

Bobwhite quail (*Colinus virginianus*): In an acute oral LD_{50} study, groups of 5 male and 5 female quails, 17 weeks old, were dosed at 0, 292, 486, 810, 1350 and 2250 mg , substance technical. Doses were administered by gavage into the stomach using corn oil. The observation period was 14 days. There were no treatment related mortalities or overt signs of toxicity at any of the dosage levels tested. A hen at the 810 mg/kg dosage level was noted as ruffled and lethargic from the morning of day 8 until study termination. The hen also showed intermittent signs of reduced reaction to external stimuli during that same period. Gross necroscopy showed an extreme loss of body mass; however, the gastrointestinal tract contained feed. The hen's condition was not considered treatment related. All other birds at all dosages were normal in appearance and behaviour throughout the test period. When compared to the controls, there were

no treatment related effects on body weights or feed consumption. A hen at the 486 mg/kg dosage and the hen that displayed clinical signs at the 810 mg/kg dosage showed declines in body weight at the day 14 body weight interval. These losses were not dose responsive and were considered incidental to treatment. In conclusion, the acute oral LD_{50} value was determined to be greater than 2250 mg/kg body weight. The no mortality level was 2250 mg/kg body weight (Lloyd et al., 1991, Doc. No.: A46539).

Japanese quail (*Coturnix coturnix japonica*): In an acute oral LD_{50} study, groups of 5 male and 5 female Japanese quails, 6 months old, were dosed at 0, 1000 and 2000 mg substance technical/kg body weight. Doses were administered by gavage into the stomach using sesame oil. The observation period was 2 weeks. No mortality and no clinical signs of intoxication was observed in any of the dosages tested. Food consumption was lower in the highest dosage until the third day after application without impact on body weight.

The LD_{50} value was higher than 2000 mg / kg body weight. The no observed effect level was established at 2000 mg/ kg body weight (Ebert and Leist, 1988a, Doc. No.: A38561).

Mallard duck (*Anas platyrhynchus*): In an acute oral LD_{50} study, groups of 5 male and 5 female Mallard ducks, 6 months old, were dosed at 0, 1000 and 2000 mg substance technical/kg body weight. The doses were administered in sesame oil into the stomach. The observation period was 14 days. No mortality and no clinical signs of intoxication were observed in any of the dosages tested. Food consumption and body weight was not influenced by the test substance. **The LD_{50} value was higher than 2000 mg/kg body weight** (Ebert, 1988a, Doc. No.: A39517).

Short-term toxicity:

Bobwhite quail : Five groups each consisting of 10 quail chicks, 10 days old at the start of treatment, received , substance technical, in the daily diet in concentrations of 562, 1000, 1780, 3160 and 5620 ppm over a period of 5 days. After this time the chicks received diet without test substance for a further 3 days. Each of the studies included 5 control groups. There were no treatment related mortalities or overt signs of toxicity at any of the concentrations tested. One bird at the 3160 ppm concentration was found dead on the afternoon of day 3. Based on necroscopy results, the mortality was not considered treatment related. All other birds were normal in appearance and behaviour throughout the study. When compared to the control, there was no effect on body weights or feed consumption at any concentration. In conclusion, the dietary LC_{50} value was

determined to be greater than 5620 ppm, equivalent to a mean daily substance intake of approx. 3476 mg/kg body weight. The no mortality level was 5620 ppm. The no observed effect concentration was 5620 ppm (Grimes et al., 1991, Doc. No.: A46675).

Japanese quail: Six groups each consisting of 10 chicks , 11 days old at the start of treatment, received , substance technical in the daily diet in concentrations of 0, 312.5, 625, 1250, 2500 and 5000 mg / kg diet (ppm) over a period of 5 days. After this time the chicks received diet without test substance for a further 3 days. One animal in the 5000 ppm group died during the night between days 4 and 5 of the study without clinical signs having been observed. In all other test groups no mortality occurred. No clinical signs of intoxication could be observed at any treatment group. Food consumption and body weight gains remained unaffected by the test substance in all treatment groups. Thus, **the LC_{50} is with certainty greater than 5000 ppm, equivalent to a mean daily substance intake of approx. 1145 mg/kg body weight.** The no observed effect level was considered to be 2500 ppm, equivalent to approximately 687 mg/kg body weight. (Ebert 1988b, Doc. No.: A39249).

Mallard duck : Six groups each consisting of 10 ducklings, 11 days old at the start of treatment, received , substance technical in the daily diet in concentrations of 0, 312.5, 625, 1250, 2500 and 5000 mg / kg diet (ppm) over a period of 5 days. After this time the chicks received diet without test substance for a further 3 days. No mortality occurred in any of the treated groups. No clinical signs of intoxication occurred in any of the dose groups at any time during the study. Food consumption and body weight gains remained unaffected by the test substance in all treatment groups. Thus, the LC_{50} is with certainty greater than 5000 ppm, equivalent to a mean daily substance intake of approx. 1676 mg/kg body weight. The no observed effect level was considered to be 5000 ppm (Ebert and Leist, 1988b, Doc. No.: A39251).

Evaluation

Classification and labelling

Substance technical must be classified as follows:

"very toxic to aquatic organisms" (R50)

"may cause long-term adverse effects in the aquatic environment" (R53)

"dangerous for the environment" (hazard symbol N)

ACTIVE SUBSTANCE:

POINT 8: DATA ON THE ECOTOXICOLOGICAL EFFECTS OF THE ACTIVE INGREDIENT

Justification for the labelling is as follows:

- high toxicity to aquatic invertebrates (EC_{50} < 1 mg/L),
- bioaccumulation potential (bioconcentration factor in fish > 100)
- lack of ready degradability

Release to the environment (soil, water) should be avoided (S61).

Furthermore . is not toxic to birds, earthworms and soil microflora but toxic to honey bees.

ACTIVE SUBSTANCE:

POINT 9: INFORMATION ON OBSERVED EFFECTS OF THE ACTIVE INGREDIENT OR PRODUCT

9 INFORMATION ON OBSERVED EFFECTS OF THE ACTIVE INGREDIENT OR PRODUCT

9.1 Incidents of exposure to the active ingredient and product

9.1.1 Humans

9.1.1.1 Investigations

No studies have been carried out on humans to date.

9.1.1.2 Observations within the company

No incidents of inadvertent exposure to have been reported to date.

9.1.2 Livestock, pets and other animals

No incidents of inadvertent exposure to have been reported to date.

9.1.3 Ornamental, agricultural and other plants

No phytotoxic properties of to agricultural crops have been observed during the development of this compound.

9.2 Practical experience on the contamination of soil water or air by:

9.2.1 Use of the product and storage of treated wood

No incidents have been reported concerning the application to treated wood, the storage of treated wood or the disposal of treated wood since the compounds first commercial use in Japan in 1992.

9.2.2 Use of treated wood

see 9.2.1

9.2.3 Disposal of treated wood and unused product

see 9.2.1

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

10 CONCLUDING EXPERT EVALUATION ON USE OF THE PRODUCT

10.1 Risks for human health

Refer to expert evaluation on product submitted by Weyl GmbH

10.2 Risks for the environment

Refer to expert evaluation on product submitted by Weyl GmbH

11 REFERENCES

Point 3:

A38037 Plant Protection / Substance Identity
Kehne
Hoechst Pfl.Fo.Chem., DEU
Ber.-Nr.: Ke288
08.04.1988

A43077 substance, pure. Density
Roechling; Rexer, K.
Hoechst C Forsch.Formulierung, DEU
Ber.-Nr.: WIR0094(06)
19.04.1990

A40002 Determination of vapour pressure as a function of temperature of
Grewer
Hoechst Angew.Phys., DEU
Ber.-Nr.: S87/1168
28.01.1988

A41447 - Solubility in water
Goerlitz, G.; Eyrich, U.; Dorn, E.
Hoechst C Produktentwicklung Oekologie 1, DEU
Ber.-Nr.: CP87/058
02.08.1989

A40028 , solubility in organic solvents
Goerlitz, G.; Eyrich, U.
Hoechst Analyt.Labor., DEU
Ber.-Nr.: CP056/88
24.11.1988

A43166 , determination of the partition coefficient n-octanol/water (log P) using HPLC
R 19900323
Weilbaecher, R.; Goerlitz, G.

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

Hoechst C Produktentwicklung Oekologie 1, DEU
23.93.1990

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

A49606 technical. Purity
Kehne
Hoechst C Forsch.Chemie, DEU
Ber.-Nr.: KE882
02.02.1993

A49801 Plant Protection / Substance Identity
Kehne
Hoechst C Forsch.Chemie, DEU
Ber.-Nr.: KE884
22.02.1993

A49802 Plant Protection / Substance Identity
Kehne
Hoechst C Forsch.Chemie, DEU
Ber.-Nr.: KE885
22.02.1993

A49607 technical. Impurities
Kehne
Hoechst C Forsch.Chemie, DEU
Ber.-Nr.: KE881
02.02.1993

A45954 , Determination of the Dissociation Constant K(Diss)
Schollmeier, M.
Hoechst C Produktentwicklung Oekologie 1, DEU
Ber.-Nr.: OE91/065
20.06.1991

A50651

Determination of the abiotic hydrolysis as a function of pH according to EPA Pesticide Assessment Guideline, Subdivision N, 161-1

Schollmeier, M.; Eyrich, U.
Hoechst C Produktentwicklung Oekologie 1, DEU
Ber.-Nr.: CP055/88

AgrEvo

A company of Hoechst and Schering

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

12.05.1993

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

A39958 Spectrum
Sarafin, R.; Lietz, G.
Hoechst Analyt.Labor., DEU
Ber.-Nr.: (B)6/89
04.01.1989

A52838 Code:
Photodegradation of 14C-labelled on Soil
Stumpf, K.; Jordan, H.J.; Buettner, B.
AgrEvo Entwicklung Umweltforschung Oekochemie, DEU
Ber.-Nr.: CB90/105
07.09.1994

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

Point 4:

A50868 Organochlorine, Organophosphorus, Nitrogen-Containing and Other Pesticides. --- Multimethod S19
DFG / Deutsche Forschungsgemeinschaft. Manual of Pesticide Residue Analysis. Ed. Hans-Peter Thier and Hans Zeumer Work (1987/1992), vol.I/II, pp. 383-400, 317-322
DFG, DEU
Ber.-Nr.: DFGS19

A53081 Studie zur Kontamination der Raumluft durch nach Behandlung von Holzoberflaechen mit Defense Anti Insect Sila (300 g/m 2)
Wampfler, W.
Eidg.Materialpruefungsanst., CHE
Ber.-Nr.: 120'309
04.03.1994

A43380 Residue determination in biological materials and soil by GC-MS (modified DFG S19 multiple residue method)
Idstein, H.; Merz, H.D.; Klug, R.;
Hoechst C Produktentwicklung Oekologie 2, DEU
Ber.-Nr.: AL015/89-0
18.04.1990

A41244 Organochlorine Pesticides and PCBs - Method 608.
Sammelmethode
EPA, USA
Ber.-Nr.: EPAMethod608
EPA608
07.1982

A45467 Residue determination of the active ingredient in fat
Idstein, H.; Ehmann, Th.; Merz, H.D.
Hoechst C Produktentwicklung Oekologie 2, DEU
Ber.-Nr.: AL11/89-2
14.02.1991

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

A45535 Determination of active ingredient residues in animal organs, tested in the liver, kidneys and brain of rats
Idstein, H.; Losse, K.; Merz, H.D.
Hoechst C Produktentwicklung Oekologie 2, DEU
Ber.-Nr.: AL010/90-0
09.11.1990

A45422 Determination of active ingredient residues in wood powder
Idstein, H.; Klug, R.; Merz, H.D.
Hoechst C Produktentwicklung Oekologie 2, DEU
Ber.-Nr.: AL016/90-0
28.12.1990

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

Point 5:

A54463 Data review and evaluation of toxicological and metabolism studies on the technical substance
Ebert, E.; Leist, K.-H.
Ber.-Nr.: 95.0402
22.06.1995

A39392 active ingredient technical
(Code: Testing for acute oral toxicity in the male and female NMRI mouse
Diehl, K.-H.; Leist, K.-H.
Hoechst Pharma Fo.To., DEU
Ber.-Nr.: 88.1744
22.12.1987

A39390 active ingredient technical
(Code: Testing for acute oral toxicity in the male and female Wistar rat
Diehl, K.-H.; Leist, K.-H.
Hoechst Pharma Fo.To., DEU
Ber.-Nr.: 88.1743
17.07.1987

A39388 - active ingredient technical
(Code: Testing for acute dermal toxicity in the male and female Wistar rat
Diehl, K.-H.; Leist, K.-H.
Hoechst Pharma Fo.To., DEU
Ber.-Nr.: 88.1742
23.07.1987

A38556 - active ingredient technical
(Code:
Testing for acute dermal toxicity in the male and female Himalayan rabbit
Diehl, K.-H.; Leist, K.-H.
Hoechst Pharma Fo.To.; DEU
Ber.-Nr.: 88.0464

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

17.03.1988

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

A37713 - active ingredient technical
(Code:
Testing for acute aerosol inhalation toxicity in the male and female SPF Wistar rat 4-hour LC50
Hofmann, T.; Jung, R.
Hoechst Pharma Fo.To., DEU
Ber.-Nr.: 88.0052
02.02.1988

A38577 - active ingredient technical
(Code:
Testing for acute intraperitoneal toxicity in the male and female Wistar rat
Diehl, K.-H.; Leist, K.-H.
Hoechst Pharma Fo.To.; DEU
Ber.-Nr.: 88.0214
02.03.1988

A39389 - active ingredient technical
(Code: Testing for primary dermal irritation in the rabbit
Diehl, K.-H.; Leist, K.-H.
Hoechst Pharma Fo.To., DEU
Ber.-Nr.: 88.1741
08.07.1987

A39391 active ingredient technical (Code:
Testing for primary eye irritation in the rabbit
Diehl, K.-H.; Leist, K.-H.
Hoechst Pharma Fo.To., DEU
Ber.-Nr.: 88.1740
13.07.1987

A38803 - active ingredient technical
(Code:
Testing for sensitising properties in the Pirbright-White guinea pig according to the technique of BUEHLER
Diehl, K.-H.; Leist, K.-H.

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

Hoechst Pharma Fo.To., DEU
Ber.-Nr.: 88.0805
15.06.1988

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

A40024 - substance technical (Code:
Testing for sensitising properties
in the Pirbright-White guinea pig in a maximisation test
Schollmeier, U.; Leist, K.-H.
Hoechst Pharma Fo.To., DEU
Ber.-Nr.: 88.1831
17.11.1988

A40579 - substance technical
(Code:
Testing for photosenisitising properties in the
Pirbright-White guinea pig
Schollmeier, U.; Leist, K.-H.
Hoechst Pharma Fo.To., DEU
Ber.-Nr.: 89.0029
16.01.1989

A40517 - substance technical (Code:
Subchronic oral toxicity - dose range finding - (28-
-day feeding study) in the Wistar rat.
Diehl, K.-H.; Leist, K.-H.
Hoechst Pharma Fo.To., DEU
Ber.-Nr.: 89.0130
26.08.1988

A42354 - substance technical (Code:
subchronic oral toxicity - dose range
finding - (28-day feeding study) in the Wistar rat
Schollmeier, U.; Leist, K.-H.
Hoechst L Toxikologie, DEU
Ber.-Nr.: 90.0007
18.01.1990

A39617 - technical substance (Code:
Testing for toxicity by repeated oral
administration to Beagle dogs (Range-finding-Test)
Brunk, R.
Hoechst Pharma Fo.To., DEU
Ber.-Nr.: 88.1274

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

26.10.1988

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

A43329 - technical substance (Code
Testing for toxicity by repeated oral administration
to Beagle dogs (Range-finding-Test)
Brunk, R.; Koenigsmann, G.; Langer, K.H.
Hoechst L Toxikologie, DEU
Ber.-Nr.: 90.0525
28.05.1990

A46430 - technical substance
(Code:
Testing for toxicity by repeated oral administration to Beagle dogs
(Range-finding-Test)
Brunk, R.
Hoechst L Toxikologie, DEU
Ber.-Nr.: 91.0880
04.08.1991

A46431 - technical substance
(Code:
Testing for toxicology by repeated
oral administration to Beagle dogs
(Range-finding-Test)
Brunk, R.
Hoechst L Toxikologie, DEU
Ber.-Nr.: 91.0882
04.08.1991

A39616 - active ingredient technical (Code:
Subchronic oral toxicity -
dose range finding - (28-day feeding study) in the NMRI mouse
Diehl, K.-H.; Leist, K.-H.
Hoechst Pharma Fo.To., DEU
Ber.-Nr.: 88.1370
18.07.1988

A46427 substance technical
(Code:
Subchronic oral toxicity - dose range finding study -
(28-day feeding study) in the NMRI mouse

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

Fischer, R.; Leist, K.-H.
Hoechst L Toxikologie, DEU
Ber.-Nr.: 91.0098
04.07.1991

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

A40925 - substance technical (Code:
Subchronic oral toxicity (13-week feeding study) in the Wistar rat
Schollmeier, U.; Leist, K.-H.
Hoechst L Toxikologie, DEU
Ber.-Nr.: 89.0128
02.02.1989

A44611 substance technical
(Code: Subchronic oral toxicity (13-week feeding study) in the Wistar rat
Schollmeier, U.; Leist, K.-H.
Hoechst L Toxikologie, DEU
Ber.-Nr.: 90.1105
04.10.1990

A46428 - substance technical
(Code:
Subchronic oral toxicity (13-week feeding study) in the Wistar rat
Fischer, R.; Leist, K.-H.
Hoechst L Toxikologie, DEU
Ber.-Nr.: 91.0879
02.08.1991

A52288 Certificate of Analysis No. AZ 05536
Hommel, K.; Goerlitz, G.
AgrEvo Entwicklung Produktanalytik, DEU
Ber.-Nr.: AZ05536
20.04.1994

A40469 substance technical (Code:
Testing for toxicity by repeated oral administration to Beagle dogs (3-month feeding study)
Brunk, R.
Hoechst Pharma Fo.To., DEU
Ber.-Nr.: 89.0057
30.01.1989

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

A46429 - substance technical
(Code:
Testing for toxicity by repeated oral administration to Beagle dogs (3-month feeding study)
Brunk, R.
Hoechst L Toxikologie, DEU
Ber.-Nr.: 91.0881
04.08.1991

A40796 - substance technical
(Code:
Subchronic oral toxicity (13-week feeding study) in the NMRI mouse
Schollmeier, U.; Leist, K.-H.
Hoechst Pharma Fo.To., DEU
Ber.-Nr.: 89.0135
25.01.1989

A46426 - substance technical
(Code:
Subchronic oral toxicity (13-week feeding study) in the NMRI mouse
Fischer, R.; Leist, K.-H.
Hoechst L Toxikologie, DEU
Ber.-Nr.: 91.0099
02.08.1991

A49451 Combined chronic toxicity / oncogenicity study by oral route (admixture with the diet) in rats
Simonnard, Alain
CIT, FRA
Ber.-Nr.: 5159TCR
92.1209
17.12.1992

A49212 - substance technical
Code:
esting for toxicity by repeated oral administration to eagle dogs (1-year feeding study)

runk, R.; Mayer, D.; Langer, K.-H.; Keil, M.
oechst L Toxikologie, DEU
Ber.-Nr.: 92.0935
09.11.1992

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

A52591 - substance technical
(Code:
Testing for toxicity by repeated oral administration to Beagle dogs (1-year feeding study)
Stammberger, I.
Hoechst L Toxikologie, DEU
Ber.-Nr.: 93.0879
21.02.1994

A49488 Combined Chronic Toxicity Oncogenicity Study by oral Route (Admixture with the Diet) in Mice
Simonnard, Alain
CIT, FRA
Ber.-Nr.: 5160TCS
92.1225
15.01.1993

A45183 Metabolism in Male and Female Rats after a Single Oral Administration of 500 mg/kg Body Weight
Buettner; Kuenzler; Kellner
Hoechst C Produktentwicklung Oekologie 1, DEU;
Hoechst Radiochem.Laboratorium, DEU
Ber.-Nr.: CM87/084
09.01.1991

A48709 . metabolism in male and female rats after a single oral administration of a nominal dose of 10 mg/kg body weight
Buettner, B.; Kuenzler, K.; Lemke, G.
Hoechst C Produktentwicklung Oekologie 1, DEU;
Hoechst C Radiochem.Laboratorium, DEU
Ber.-Nr.: CM87/082
22.06.1992

A41503 Kinetics in the rat after single oral administration of 500 mg/kg body weight
Eckert, H.G.; Kellner, H.-M.
Hoechst Radiochem.Laboratorium, DEU
Ber.-Nr.: 01-L42-0563-89

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

22.05.1989

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

A44064

Kinetics in the rat after single oral administration of 100 mg/kg body weight
Eckert, H.G.; Kellner, H.-M.
Hoechst Radiochem.Laboratorium, DEU
Ber.-Nr.: 01-L42-0573-90
28.05.1990

A50094

Kinetics in the rat: excretion and tissue distribution at different times after a single oral dose of 10 mg/kg or 500 mg/kg to male and female rats
Kellner, H.-M.; Puttkamer, G.-D. von
Hoechst Radiochem.Laboratorium, DEU
Ber.-Nr.: O1-L42-0646-92
19.03.1993

A51063

Kinetics in the rat: excretion and tissue distribution at different times after ten daily oral doses of 10 mg/kg and 500 mg/kg to male and female rats
Kellner, H.-M.
Hoechst RCL, DEU
Ber.-Nr.: 01-L42-0686-93
29.07.1993

A48709

metabolism in male and female rats after a single oral administration of a nominal dose of 10 mg/kg body weight
Buettner, B.; Kuenzler, K.; Lemke, G.
Hoechst C Produktentwicklung Oekologie 1, DEU;
Hoechst C Radiochem.Laboratorium, DEU
Ber.-Nr.: CM87/082
22.06.1992

A49560

Dermal absorption in rat following a single topical application of test substance at dose levels of 0.001, 0.01 and 0.1 mg cm-2 skin
Till, C.P.
Hoechst UK, GBR

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

Ber.-Nr.: CT1D051192
05.11.1992

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

A48022 ruminant feeding study (pretest)
Zietz, E.; Spranz, E.
Battelle, DEU
Ber.-Nr.: BE-MT-08-90-01-CSO-02
08.04.1992

A48907 : Distribution, degradation, metabolism and excretion after repeated oral administration to a lactating goat
Van Dijk, A.
Res.Consult.Comp., CHE
Ber.-Nr.: RCC285434
09.09.1992

A54407
Summary and evaluation of toxicokinetics, metabolism and bioaccumulation in the animal organism
Stumpf, K.
AgrEvo Entwicklung Umweltforschung Oekochemie, DEU
Ber.-Nr.: OE93/082
02.06.1995

A36830 - substance, technical (Code:
Study of the mutagenic potential in strains of Salmonella typhimurium (Ames Test) and Escherichia coli
Mueller, W.
Hoechst Pharma Fo.To., DEU
Ber.-Nr.: 87.1437
17.09.1987

A38558 substance, technical
(Code:
Detection of gene mutations in somatic cells in culture HGPRT-test with V79 cells
Mueller, W.; Mayer
Hoechst Pharma Fo.To.; DEU
Ber.-Nr.: 88.0510
18.04.1988

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

A40038 Chromosome aberration assay in human lymphocytes in vitro with
o.A.
Cytotest Cell Res., DEU
Ber.-Nr.: GT88.1276
120600
04.08.1988

A40039 Chromosome Aberration Assay in Human Lymphocytes in vitro with
Cytotest Cell Res., DEU
Ber.-Nr.: GT88.1276
22.11.1988

A42116 Chromosome aberration assay in human lymphocytes in vitro with
Voelkner, W.; Heidemann, A.
Cytotest Cell Res., DEU
Ber.-Nr.: 89.1654
21.11.1989

A44855 DNA Repair Test of
in Bacillus subtilis
Ohtsuka, Masanori
Chem.Biotest.Cent., JPN
Ber.-Nr.: T-236E
91.0083
03.10.1990

A39978 Mitotic Gene Conversion in Saccharomyces cerevisiae D4
Test Substance: Technical
(Code:
LSR-RTC Report No.: 157026-M-01888
Nunziata, A.
Life Sci.Res., ITA
Ber.-Nr.: GT88.1997
08.11.1988

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

A42884 Mitotic Gene Conversion in Saccharomyces cerevisiae D4. Addendum to Final Report.
Forster, R.
Life Sci.Res., ITA
Ber.-Nr.: 157026-M-01888
13.03.1990

A38559 Evaluation of in the unscheduled DNA synthesis test in mammalian cells in vitro
Kramer; Mueller; Mayer
Hoechst Pharma Fo.To.; DEU
Ber.-Nr.: 88.0219
25.02.1988

A38802 substance, technical
(Code:
Micronucleus test in male and female NMRI mice after oral administration
Mueller, W.; Mayer
Hoechst Pharma Fo.To., DEU
Ber.-Nr.: 88.0646
17.05.1988

A39670 Chromosome Aberration Assay in Bone Marrow Cells of the Chinese Hamster with
Voelkner, Wolfgang; Mueller, Ewald
Cytotest Cell Res., DEU
Ber.-Nr.: 127506
88.1322
12.08.1988

A39671 Chromosome aberration assay in bone marrow cells of the Chinese hamster with
Mueller, E.W.; Voelkner, W.
Cytotest Cell Res., DEU
Ber.-Nr.: 127506
31.10.1988

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

A49556 Substance Technical
(Code:
Preliminary Study to the Two-Generation Reproduction Study in the Rat
Dotti, A.; Kinder, J.; Biedermann, K.
RCC, CHE
Ber.-Nr.: 93.0011
21.01.1993

A49487 Substance Technical
(Code:
Two-Generation Reproduction Study in the Rat
Dotti, A.; Kinder, J.; Biedermann, K.
RCC, CHE
Ber.-Nr.: 258996
92.1224
03.09.1991

A51275 Two-generation reproduction study with substance technical (Code:
Statement concerning definition of the NOEL (no observed effect level)
Dotti, A.; Thouin, M.
RCC, CHE
Ber.-Nr.: 258996
03.09.1993

A54529 Male rats of the P generation of a two-generation reproduction study: determination of testosterone and progesterone in plasma after dietary administration of substance technical
(Code:
Burri, R.
RCC, CHE
Ber.-Nr.: 351292
14.06.1995

A40312 - substance technical
(Code:
Testing for embryotoxicity in the Wistar rat after

oral administration (limit test)
Baeder, Ch.
Hoechst L Toxikologie, DEU
Ber.-Nr.: 89.0139
30.12.1989

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

A46834 · substance technical
(Code:
Testing for embryotoxicity and effects on post-natal development in Wistar rats after oral administration (limit test)
Albrecht, M.; Baeder, Ch.
Hoechst L Toxikologie, DEU
Ber.-Nr.: 91.0928
27.09.1991

A40311 - substance technical
(Code_
Testing for embryotoxicity in the Himalayan rabbit after oral administration (limit test)
Baeder, Ch.
Hoechst L Toxikologie, DEU
Ber.-Nr.: 89.0140
22.12.1989

A44205 - substance, technical
(Code:
Testing for embryotoxicity in the Himalayan rabbit after oral administration
Albrecht, M.; Baeder, Ch.
Hoechst L Toxikologie, DEU
Ber.-Nr.: 90.0918
20.08.1990

A45316 - substance technical (Code:
Testing for acute delayed neurotoxicity in white Leghorn hens
Ebert, E.
Hoechst L Toxikologie, DEU
Ber.-Nr.: 90.1398
07.02.1991

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

Point 6:

A53081 Studie zur Kontamination der Raumluft durch
nach Behandlung von Holzoberflaechen mit
Defense Anti Insect Sila (300 g/m 2)
Wampfler, W.
Eidg.Materialpruefungsanst., CHE
Ber.-Nr.: 120'309
04.03.1994

A40002 Determination of vapour pressure as a function of temperature of
Grewer
Hoechst Angew.Phys., DEU
Ber.-Nr.: S87/1168
28.01.1988

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

Point 7:

A49193 Aerobic Soil Metabolism Study
Schwab, W.; Gildemeister, H.; Rockmann, S.
Hoechst C Produktentwicklung Oekologie 1, DEU
Ber.-Nr.: CB88/060
02.11.1992

A49300 Anaerobic Degradation in Soil
Schwab, W.; Gildemeister, H.; Von Fleischbein, I.
Hoechst C Produktentwicklung Oekologie 1, DEU
Ber.-Nr.: CB88/073
16.12.1992

A49239 , Aerobic Aquatic Metabolism
Schwab, W.; Gildemeister, H.; Von Fleischbein, I.
Hoechst C Produktentwicklung Oekologie 1, DEU
Ber.-Nr.: CB88/072
24.11.1992

A54708 1st Amendment to Report CB88/072

A46678 - adsorption to soil
A provisional assessment
Goerlitz, G.
Hoechst C Produktentwicklung Oekologie 1, DEU
Ber.-Nr.: OE91/018
01.02.1991

A44748 Examination of the leaching behaviour in the LUFA standard soils 2.1, 2.2 and 2.3 in accordance with BBA Guidline IV, 4-2
Buettner, B.; Kuenzler, K.; Lemke, G.
Hoechst C Produktentwicklung Oekologie 1, DEU
Ber.-Nr.: CB89/084
19.03.1990

A40437 Flow-through Bioaccumulation and Metabolism Study with Bluegill Sunfish (Lepomis macrochirus)

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

Buettner, B.; Haberkorn, B.; Fischer, R.
Hoechst Analyt.Labor., DEU; Hoechst Pfl.Fo.Biol., DEU
Ber.-Nr.: CM028/88
21.11.1988

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

Point 8:

A43486 - substance, technical

Effect to Scenedesmus subspicatus (Green alga)
in a Growth Inhibition Test (method OECD)
Fischer, R.
Hoechst C Produktentwicklung Oekologie 1, DEU
Ber.-Nr.: CE89/037
01.06.1990

A44380 The effect of - substance, technical
(Identification code: on
Daphnia magna (water flea) in a static-acute toxicity test
Test No. Dm655/a+b (Method OECD)
Fischer, R.
Hoechst Pfl.Fo.Biol., DEU
Ber.-Nr.: OEK87/130D
22.09.1987

A49194 Effect to Daphnia magna
(Waterflea) in a Life-Cycle (21-day static renewal) Chronic
Toxicity Test (method EPA)
Heusel, R.
Hoechst C Produktentwicklung Oekologie 1, DEU
Ber.-Nr.: CE89/052
11.11.1992

A54655 96-hour Acute Toxicity of to Palaemon aucidens
Chemical Biotesting Center, JPN
Ber.-Nr.: E90-0867E
10.1991

A43501 - substance, technical

Effect to Cyprinus carpio (Mirror carp)
in a Static-Acute Toxicity Test (method OECD)
Fischer, R.
Hoechst C Produktentwicklung Oekologie 1, DEU

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

Ber.-Nr.: CE89/038
01.06.1990

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

A43500 substance, technical

Effect to
Lepomis macrochirus (Bluegill sunfish)
in a Static-Acute Toxicity Test (method EPA)
Fischer, R.
Hoechst C Produktentwicklung Oekologie 1, DEU
Ber.-Nr.: CE89/039
01.06.1990

A43502 substance, technical

Effect to Salmo gairdneri (Rainbow trout)
in a Static-Acute Toxicity Test (method EPA)
Fischer, R.
Hoechst Produktentwicklung Oekologie 1, DEU
Ber.-Nr.: CE89/040
01.06.1990

A48467 (substance technical)

(Code:
Investigating the short-term effect on aerobic soil respiration (in accordance with BBA, VI, 1-1)
Baedelt, H.; Frings, H.
Hoechst C Produktentwicklung Oekologie 2, DEU
Ber.-Nr.: CW92/123
14.07.1992

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

A40219 - substance, technical grade
(Code:
Investigation into the effect of
on the nitrification of ammonium sulphate
Altmannsberger, K.; Baedelt, H.; Frings, H.
Hoechst LEA, DEU
Ber.-Nr.: LEA-A-88-076D
10.11.1988

A38801 The Effect of - substance, technical
(Identification code :
to Eisenia fetida (Earthworm) in a 14 day Artificial
Soil Test (method OECD)
Fischer, R.; Schulze, E.-F.
Hoechst Pfl.Fo.Biol., DEU
Ber.-Nr.: OEK88/080E
03.07.1988

A39979 Report on Laboratory Investigations into the Oral and
Contact Toxicity of to the
Honey Bee Apis mellifera L.
Bock, K.-D.
Hoechst LEA, DEU
Ber.-Nr.: LEA/I88/005
17.11.1988

A46539 an acute oral toxicity study with the
bobwhite. Final report.
Lloyd, Donna; Hoxter, Kimberly; Smith, Gregory J.
Wildl.Int., USA
Ber.-Nr.: 91.0945
30.01.1991

A38561 - active ingredient technical
(Code:
Testing for acute oral toxicity in the male and
female japanese quail (Coturnix coturnix japonica)
Ebert, E.; Leist, K.-H.
Hoechst Pharma Fo.To.; DEU

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

Ber.-Nr.: 88.0117
22.02.1988

ACTIVE SUBSTANCE:

POINT 11: REFERENCES

A39517 active ingredient technical
(Code: Testing for acute oral toxicity in the male and female Mallard Duck (Anas platyrhynchos)
Ebert, E.
Hoechst Pharma Fo.To., DEU
Ber.-Nr.: 88.1863
04.02.1988

A46675 : A dietary LC50 study with the bobwhite
Grimes, Jennie; Hoxter, Kimberly; Jaber, Mark
Wildl.Int., USA
Ber.-Nr.: 125-149
91.1018
30.01.1991

A39249 - active ingredient technical
(Code:
8-day dietary LC50 test in the Japanese quail (Coturnix coturnix Japonica)
Ebert, E.
Hoechst Pharma Fo.To., DEU
Ber.-Nr.: 88.0986
27.06.1988

A39251 - active ingredient technical
(Code:
8-day dietary LC50 test in the mallard duck (Anas platyrhynchos)
Ebert, E.; Leist, K.-H.
Hoechst Pharma Fo.To., DEU
Ber.-Nr.: 88.0779
16.06.1988

ACTIVE SUBSTANCE:

CONTENT

ACTIVE SUBSTANCE:

CONTENT

ACTIVE SUBSTANCE:

CONTENT

TRIAGE of 8(e) Submissions

Date sent to triage: _____ (NON-CAP) CAP

Submission number: 13905 A TSCA Inventory: Y (N) D

STUDY TYPE (circle appropriate):

Ernest ~~Falke~~ (E605C)
(ATOX) (SBTOX) (SEN) (CARC)

Gordon ~~Cash~~ (E425)
(ECO) (~~AQUATO~~)

Katherine ~~Anitole~~ (E613B)
(RTOX/DTOX)

Daljit ~~Sawhney~~ (E611A)
(CTOX) (STOX)

Deborah Norris (E606)
NEUR

Elizabeth Margosches (E613C)
EPI

Michael ~~Cimino~~ (E611D)
(GTOX)

Leonard ~~Keifer~~ (E611C)
(Metabolism/Pharmacokinetics)

OTHER: _____

NOTES:

CECATS/TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ-C497-13905 S SEQ A

TYPE: (INT) SUPP FLWP

SUBMITTER NAME:
AgrEvo

SUB. DATE: 3-14-97 OTS DATE: — CSRAD DATE: 4-27-97

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639 REFER TO CHEMICAL SCREENING)
0678 CAP NOTICE

VOLUNTARY ACTIONS
0401 NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKER/OTHERS
(0404 LABEL/MSDS CHANGES)
0405 PROCESS/HANDLING CHANGES
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

CHEMICAL NAME:
Confident

CAS#
Confident

INFORMATION TYPE:		P	F	C
0201	ONCO (HUMAN)	01	02	04
(0202)	ONCO (ANIMAL)	(01	02	04)
0203	CELL TRANS (IN VITRO)	01	02	04
(0204)	MUTA (IN VITRO)	(01	02	04)
(0205)	MUTA (IN VIVO)	(01	02	04)
0206	REPRO/TERATO (HUMAN)	01	02	04
(0207)	REPRO/TERATO (ANIMAL)	(01	02	04)
0208	NEURO (HUMAN)	01	02	04
0209	NEURO (ANIMAL)	01	02	04
0210	ACUTE TOX. (HUMAN)	01	02	04
0211	CHR. TOX. (HUMAN)	01	02	04
(0212)	ACUTE TOX. (ANIMAL)	(01	02	04)
[redacted]	SUB ACUTE TOX (ANIMAL)	(01	02	04)
0214	SUB CHRONIC TOX (ANIMAL)	(01	02	04)
(0215)	CHRONIC TOX (ANIMAL)	(01	02	04)

INFORMATION TYPE:		P	F	C
0216	EPYCLIN	01	02	04
0217	HUMAN EXPOS (PROD CONTAM)	01	02	04
0218	HUMAN EXPOS (ACCIDENTAL)	01	02	04
0219	HUMAN EXPOS (MONITORING)	01	02	04
(0220)	ECO/AQUA TOX	(01	02	04)
0221	ENV. OCCC/REL/FATE	01	02	04
0222	EMER INCI OF ENV CONTAM	01	02	04
0223	RESPONSE REQEST DELAY	01	02	04
[redacted]	PROD/COMP/CHEM ID	01	02	04
0225	REPORTING RATIONALE	01	02	04
0226	CONFIDENTIAL	01	02	04
0227	ALLERG (HUMAN)	01	02	04
(0228)	ALLERG (ANIMAL)	(01	02	04)
(0239	METAB/PHARMACO (ANIMAL)	(01	02	04)
0240	METAB/PHARMACO (HUMAN)	01	02	04

INFORMATION TYPE:		P	F	C
0241	IMMUNO (ANIMAL)	01	02	04
0242	IMMUNO (HUMAN)	01	02	04
(0243)	CHEM/PHYS PROP	01	02	04
(0244	CLASTO (IN VITRO)	(01	02	04
0245	CLASTO (ANIMAL)	01	02	04
[redacted]	CLASTO (HUMAN)	(01	02	04
0247	DNA DAM/REPAIR	01	02	04
[redacted]	PROD/USE/PROC	01	02	04
0251	MSDS	01	02	04
0299	OTHER	01	02	04

TRIAGE DATA: NON-CBI INVENTORY

YES

CAS SR (NO)

IN TRIAGE

ONGOING REVIEW

YES (DROP/REFER)

NO (CONTINUE)

REFER

SPECIES

RAT
DOG
MOUS
RBT
GOAT
DAPH
BEE
COW
GP

TOXICOLOGICAL CONCERN:

LOW

MED

HIGH

USE:

exp. chem.

PRODUCTION:

ENTRY FORM

CAPNUM	LTR	DATE	CBI	CASNO	CONCERN	AI	SOLUBILITY
13905	a	0497	s	CONFIDE	LOW	>91	0.001mg/l

CHEMNAME

Non-ester pyrethoid

PHYSTATE

liquid

MELTINGPT

NS

ORGANISM	DURATION	ENDPOINT	CODE	TOXVALUE	UNITS
Algae, S. subspicatus	72h	EC50	>	910	mg/l

COMMENTS

Growth inhib.
72hNOEC=910mg/l
nominal,acetone

ENTRY FORM

CAPNUM	LTR	DATE	CBI	CASNO	CONCERN	AI	SOLUBILITY
13905	a	0497	s	CONFIDE	HIGH	>91	0.001mg/l

CHEMNAME

Non-ester pyrethoid, static

PHYSTATE

liquid

ORGANISM	DURATION	ENDPOINT	CODE	TOXVALUE	UNITS
Water flea, Daphnia magna	48h	EC50		0.0036	mg/l

MELTINGPT

NS

COMMENTS

48hNOEC=0.00016mg/l
24hEC50=0.063mg/l

ENTRY FORM

CAPNUM	LTR	DATE	CBI	CASNO	CONCERN	AI	SOLUBILITY
13905	a	0497	s	CONFIDE	HIGH	>91	0.001mg/l

CHEMNAME

Non-ester pyrethoid

PHYSTATE

liquid

ORGANISM	DURATION	ENDPOINT	CODE	TOXVALUE	UNITS
Water flea, Daphnia magna	21d	NOEC		0.051	ug/l

MELTINGPT

NS

COMMENTS

(repro., immob., growth, embryo devel.)
acetone

ENTRY FORM

CAPNUM	LTR	DATE	CBI	CASNO	CONCERN	AI	SOLUBILITY
13905	a	0497	s	CONFIDE	HIGH	>91	0.001mg/l

CHEMNAME

Non-ester pyrethoid, flow-through

PHYSTATE

liquid

ORGANISM	DURATION	ENDPOINT	CODE	TOXVALUE	UNITS
Freshwater shrimp, P. aucidens	96h	LC50		0.00426	mg/l

MELTINGPT

NS

COMMENTS

48hLC50=0.018mg/l

ENTRY FORM

CAPNUM	LTR	DATE	CBI	CASNO	CONCERN	AI	SOLUBILITY
13905	a	0497	s	CONFIDE	LOW	>91	0.001mg/l

CHEMNAME

Non-ester pyrethoid, static

PHYSTATE

liquid

ORGANISM	DURATION	ENDPOINT	CODE	TOXVALUE	UNITS
Mirror carp, C. carpio	96h	LC50	>	910	mg/l

MELTINGPT

NS

COMMENTS

96hNOEC=180mg/l (intoxication)
96hLOEC=320mg/l

ENTRY FORM

CAPNUM	LTR	DATE	CBI	CASNO	CONCERN	AI	SOLUBILITY
13905	a	0497	s	CONFIDE	MODERA	>91	0.001mg/l

CHEMNAME

Non-ester pyrethoid, static

PHYSTATE

liquid

ORGANISM	DURATION	ENDPOINT	CODE	TOXVALUE	UNITS
Bluegill, L. macrochirus	96h	LC50	>	91	mg/l

MELTINGPT

NS

COMMENTS

96hLC50>91<910mg/l
96hNOEC=56mg/l(Intoxication)

ENTRY FORM

CAPNUM	LTR	DATE	CBI	CASNO	CONCERN	AI	SOLUBILITY
13905	a	0497	s	CONFIDE	LOW	>91	0.001mg/l

CHEMNAME

Non-ester pyrethoid, static

PHYSTATE

liquid

ORGANISM	DURATION	ENDPOINT	CODE	TOXVALUE	UNITS
Rainbow trout, O. mykiss	96h	LC50	>	910	mg/l

MELTINGPT

NS

COMMENTS

96hNOEC=51mg/l
TWEEN 80

ENTRY FORM

CAPNUM	LTR	DATE	CBI	CASNO	CONCERN	AI	SOLUBILITY
13905	a	0497	S	CONFIDE		>91	0.001mg/l

CHEMNAME

Non-ester pyrethoid, flow-through

PHYSTATE

liquid

ORGANISM	DURATION	ENDPOINT	CODE	TOXVALUE	UNITS
Bluegill snfish,L machrochirus	21d	BCF		824	

MELTINGPT

NS

COMMENTS

ENTRY FORM

CAPNUM	LTR	DATE	CBI	CASNO	CONCERN	AI	SOLUBILITY
13905	a	0497	s	CONFIDE	LOW	>91	0.001mg/l

CHEMNAME

Non-ester pyrethoid

PHYSTATE

liquid

ORGANISM	DURATION	ENDPOINT	CODE	TOXVALUE	UNITS
Earthworm, Eisenia fetida		LC50	>	910	mg/kg

MELTINGPT

NS

COMMENTS

NOEC=910mg/kg

ENTRY FORM

CAPNUM	LTR	DATE	CBI	CASNO	CONCERN	AI	SOLUBILITY
13905	a	0497	s	CONFIDE		>91	0.001mg/l

CHEMNAME

Non-ester pyrethoid

PHYSTATE

liquid

ORGANISM	DURATION	ENDPOINT	CODE	TOXVALUE	UNITS	MELTINGPT
Honey bees, Apis mellifera	48h	LD50		0.434		NS

COMMENTS

48hLD50=0.434ug/bee(oral)
24hLD50=0.02 (contact)

ENTRY FORM

CAPNUM	LTR	DATE	CBI	CASNO	CONCERN	AI
13905	a	0497	s	CONFIDE	LOW	>91

SOLUBILITY: 0.001mg/l

CHEMNAME: Non-ester pyrethoid

PHYSTATE: liquid

ORGANISM	DURATION	ENDPOINT	CODE	TOXVALUE	UNITS
Bobwhite quail, C. virginianus	14d	LD50	>	2048	mg/kg

MELTINGPT: NS

COMMENTS: NOEL=2048 mg/kg
corn oil

ENTRY FORM

CAPNUM	LTR	DATE	CBI	CASNO	CONCERN	AI
13905	a	0497	s	CONFIDE	LOW	>91

SOLUBILITY: 0.001mg/l

CHEMNAME: Non-ester pyrethoid

PHYSTATE: liquid

ORGANISM	DURATION	ENDPOINT	CODE	TOXVALUE	UNITS
Japanese quail, C. japonica	14d	LD50	>	1820	mg/kg

MELTINGPT: NS

COMMENTS: NOEL=1820 mg/kg
sesame oil

ENTRY FORM

CAPNUM	LTR	DATE	CBI	CASNO	CONCERN	AI	SOLUBILITY
13905	a	0497	s	CONFIDE	LOW	>91	0.001mg/l

CHEMNAME

Non-ester pyrethoid

PHYSTATE

liquid

ORGANISM	DURATION	ENDPOINT	CODE	TOXVALUE	UNITS	MELTINGPT
Bobwhite quail, C. virginianus	8d	LC50	>	3163	mg/kg	NS

COMMENTS

NOEL=3163 mg/kg
admin. in diet

ENTRY FORM

CAPNUM	LTR	DATE	CBI	CASNO	CONCERN	AI
13905	a	0497	s	CONFIDE	LOW	>91

SOLUBILITY: 0.001mg/l

CHEMNAME: Non-ester pyrethoid

PHYSTATE: liquid

ORGANISM	DURATION	ENDPOINT	CODE	TOXVALUE	UNITS
Japanese quail, C. japonica	8d	LC50	>	1042	mg/kg

MELTINGPT: NS

COMMENTS

NOEL=625 mg/kg
admin. in diet

ENTRY FORM

CAPNUM	LTR	DATE	CBI	CASNO	CONCERN	AI
13905	a	0497	s	CONFIDE	LOW	>91

SOLUBILITY: 0.001m/l

CHEMNAME: Non-ester pyrethoid

PHYSTATE: liquid

ORGANISM	DURATION	ENDPOINT	CODE	TOXVALUE	UNITS
Mallard duck, A. platyrhynchus	8d	LC50	>	1525	mg/kg

MELTINGPT: NS

COMMENTS

NOEL=1525 mg/kg
Admin. in diet

AgrEvo™

MR 5026

Certified Mail P1856782452
Return Receipt

March 18, 1998

PDCN: 88970000155
8EHQ - 0398 - 13905

Contains No CBI

Document Control Officer (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Re: Document Control Number 8EHQ-97-13905

To Whom It May Concern:

AgrEvo Environmental health, Inc., Montvale, new Jersey, has recently been notified from our overseas laboratories that there appears to have been additional reproductive effects in the rat and bobwhite quail studies, which have not yet been finalized.

AgrEvo wishes to advise the Agency that, based on this data at this time, we have no plans for further commercialization of the product.

If you have further questions, please contact me.

Sincerely yours,

Joseph A. Conti
Manager, Registration

JAC/r
Epatsca

Cc: K. Chisholm

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OPPT CBIC
98 MAR 23 PM 2:47

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OPPT NCIC
98 MAR 30 AM 8:03

AgrEvo Environmental Health
95 Chestnut Ridge Road · Montvale NJ 07645 · Tel. (201)307-9700 · Fax: (201)307-3281